“INCIDENCE AND CLINICAL FEATURES OF ETHAMBUTOL - INDUCED OPTIC NEUROPATHY IN TUBERCULAR UVEITIS PATIENTS”

DISSERTATION SUBMITTED FOR

MS (Branch III) Ophthalmology

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CERTIFICATE

This is to certify that this dissertation entitled "**INCIDENCE AND CLINICAL FEATURES OF ETHAMBUTOL - INDUCED OPTIC NEUROPATHY IN TUBERCULAR UVEITIS PATIENTS"** is a bonafide work done by **Dr.Swathija B** under our guidance and supervision in the Uvea Services of Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Madurai during the period of her Postgraduate training in Ophthalmology for July 2013 – April 2016.

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DECLARATION

I, **Dr.Swathija B** hereby declare that this dissertation entitled, **"INCIDENCE AND CLINICAL FEATURES OF ETHAMBUTOL - INDUCED OPTIC NEUROPATHY IN TUBERCULAR UVEITIS PATIENTS"** is being submitted in partial fulfilment for the award of MS degree in Ophthalmology by The Tamilnadu Dr.MGR Medical University in the examination to be held in April 2016.

I declare that this dissertation is my original work and has not formed the basis for the award of any other degree or diploma award to me previously.

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CONTENTS

INTRODUCTION

Tuberculosis caused by bacteria *Mycobacterium tuberculosis* complex is one of the oldest diseases and still a major cause of death worldwide. The disease usually affects lungs, but other organs including eye can be affected. Ocular tuberculosis is one of the most important causes for Uveitis. Ocular tuberculosis can be primary, where the eye is the initial port of entry, or secondary, where the organisms spread to the eye hematogenously. When properly treated, tuberculosis caused by drug-susceptible strains of bacteria is curable in almost all cases.

Tuberculosis remains a major health problem. In 2012WHO report stated "an estimated 8.6 million people developed TB and 1.3 million died from the disease. India and China alone accounted for 26% and 12% of global cases respectively".[2]

Close to 80% of tuberculosis occurs in the lungs , but ocular TB is one of the most important extra pulmonary manifestations[3]. Intraocular tuberculosis can happen without clinical activity in other parts of body and may resemble several clinical entities[4] .Uveitis is the most common manifestation of intraocular TB and the most common clinical presentation appears to be

posterior uveitis , followed by anterior uveitis, panuveitis , and intermediate uveitis.[5]

By definition uveitis implies inflammation of iris, ciliary body and choroid.[6]. There is no well defined criteria for diagnosis of intraocular TB[5,8]. Chest x-ray, mantoux test, sputum microscopy and culture, PCR technique , quantiferon TB gold technique (IGRA)[9] positron emission topography [10] , serum antipurified cord factor antibodies [11] and histo-pathological studies are available diagnostic modalities with their own limitations. However with the help of different modalities, better visual and systemic outcomes can be expected. In our study we will be following the guidelines given by Gupta et al.[3,5]

For the inflammation associated with ocular TB treatment is given to treat both infection and inflammation.[12,13]

Simultaneous infection by HIV greatly increases the risk of developing active tuberculosis and concomitant treatment with ART and ATT[14] can result in immune reconstitution inflammatory syndrome (IRIS)[15,16] which makes the situation more difficult.

EPIDEMIOLOGY

Control of Tuberculosis in India is a big challenge. The burden of tuberculosis in India was always high and is still on rise. Every year, 1.8 million persons develop the disease, of which about 800,000 are infectious; and, until recently, 370,000 died of it annually -1,000 every day. The disease is a serious barrier economic and social barrier. An estimate of 100 million workdays is lost due to illness. Society and the country also incur a huge cost due to TB-nearly US$ 3 billion in indirect costs and US$ 300 million in direct costs.[16,17,18]

MYCOBACTERIUM TUBERCULOSIS

Tubercle bacillus or Koch's bacillus (named after discovery of the organism by Robert Koch in 1882) called *Mycobacterium tuberculosis* causes tuberculosis in the lungs and other tissues of the human body. The organism is a strict aerobe and thrives best in tissues with high oxygen tension such as in the apex of the lung. Out of various pathogenic strains for human disease included in Mycobacterium tuberculosis complex, currently most common is M. tuberculosis hominis (human strain), while M. tuberculosis bovis (bovine strain) used to be common pathogen to human beings during the era of consumption of unpasteurised milk but presently constitutes a small number of human cases. Other less common strains included in the complex are M. africanum (isolated from patients from parts of Africa), M. microti, M. pinnipedii and M. canettii. A nonpathogenic strain, M. smegmatis, is found in the smegma and as contaminant in the urine of both men and women.

M. tuberculosis hominis is a slender rod-like bacillus, 0.5 μm by 3 μm, is neutral on Gram staining, and can be demonstrated by the following methods:

1. Acid fast (Ziehl-Neelsen) staining. The acid fastness of the tubercle bacilli is due to mycolic acids, cross-linked fatty acids and other lipids in the cell wall of the organism making it impermeable to the usual stains. It takes up stain by

heated carbol fuchsin and resists decolourisation by acids and alcohols (acid fast and alcohol fast) and can be decolourised by 20% sulphuric acid (compared to 5% sulphuric acid for declourisation for M. leprae which are less acid fast)

1. False positive AFB staining is seen due to Nocardia, Rhodococcus, Legionella, and some protozoa such as Isospora and Cryptosporidium.
2. Fluorescent dye methods.
3. Culture of the organism from sputum in Lowenstein- Jensen (L.J.) medium for 6 weeks.
4. Guinea pig inoculation method by subcutaneous injection of the organisms.
5. Molecular methods such as PCR are the most recent methods.

HIV-ASSOCIATED TUBERCULOSIS:

HIV-infected individuals have very high incidence of tuberculosis all over the world. Vice-versa, rate of HIV infection in patients of tuberculosis is very high. Moreover, HIV-infected individual on acquiring infection with tubercle bacilli develops active disease rapidly (within few weeks) rather than after months or years. Pulmonary tuberculosis in HIV presents in typical manner. However, it is more often sputum smear negative but often culture

positive. Extra-pulmonary tuberculosis is more common in HIV disease and manifests commonly by involving lymph nodes, pleura, pericardium, and tuberculous meningitis. Infection with M. avium-intracellulare (avian or bird strain) is common in patients with HIV/AIDS.

MODES OF TRANSMISSION

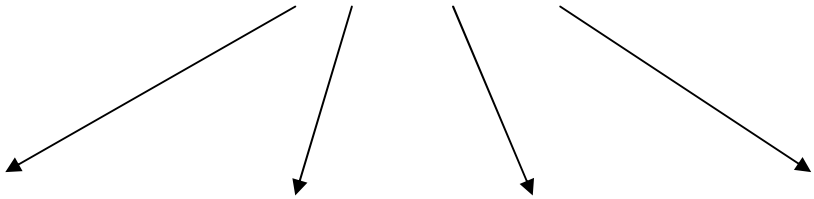
Human beings acquire infection with tubercle bacilli by one of the following routes:

INHALATION	INGESTION	INOCULATION	TRANSPLACENTAL
Via fresh infective droplets or dried sputum	Via self swallowing of infective sputum or consuming milk infected with bovine TB bacilli	Via inoculation of organism in to skin	Congenital tuberculosis , spread from infected mother to foetus; very rare

SPREAD OF TUBERCULOSIS

The disease spreads in the body by various routes:

VARIOUS WAYS OF SPREAD



Local spread	lymphatic spread	haematogenous	via natural passages
By 1.transbronchial Macrophages to Surrounding Tissues.	to lymphoid follicles in various Parts of body	by tuberculous bacillaemia	spread 2.spread to peritone al Cavity from Salphingitis etc;

Tuberculin (Mantoux) skin test:

This test is done by intradermal injection of 0.1 ml of tuberculoprotein, purified protein derivative (PPD). Delayed type of hypersensitivity develops in individuals who are having or have been previously infected with tuberculous infection which is identified as an indurated area of more than 15 mm in 72 hours. However, patients having disseminated tuberculosis may show negative test due to release of large amount of tuberculoproteins from the endogenous lesions masking the hypersensitivity test. A positive test is indicative of cellmediated hypersensitivity to tubercular antigens but does not distinguish between infection and disease. The test may be false positive in atypical mycobacterial infection and false negative in sarcoidosis, some viral infections, Hodgkin's disease and fulminant tuberculosis.

Immunisation against tuberculosis:

Protective immunization against tuberculosis is induced by injection of attenuated strains of bovine type of tubercle bacilli, *Bacille Calmette-Guérin* (BCG). Cell-mediated immunity with consequent delayed hypersensitivity reaction develops with healing of the lesion, but the cell-mediated immunity persists, rendering the host tuberculin-positive and hence immune.

EVOLUTION OF TUBERCLE

The sequence of events which take place when tubercle bacilli are introduced into the tissue are as under:

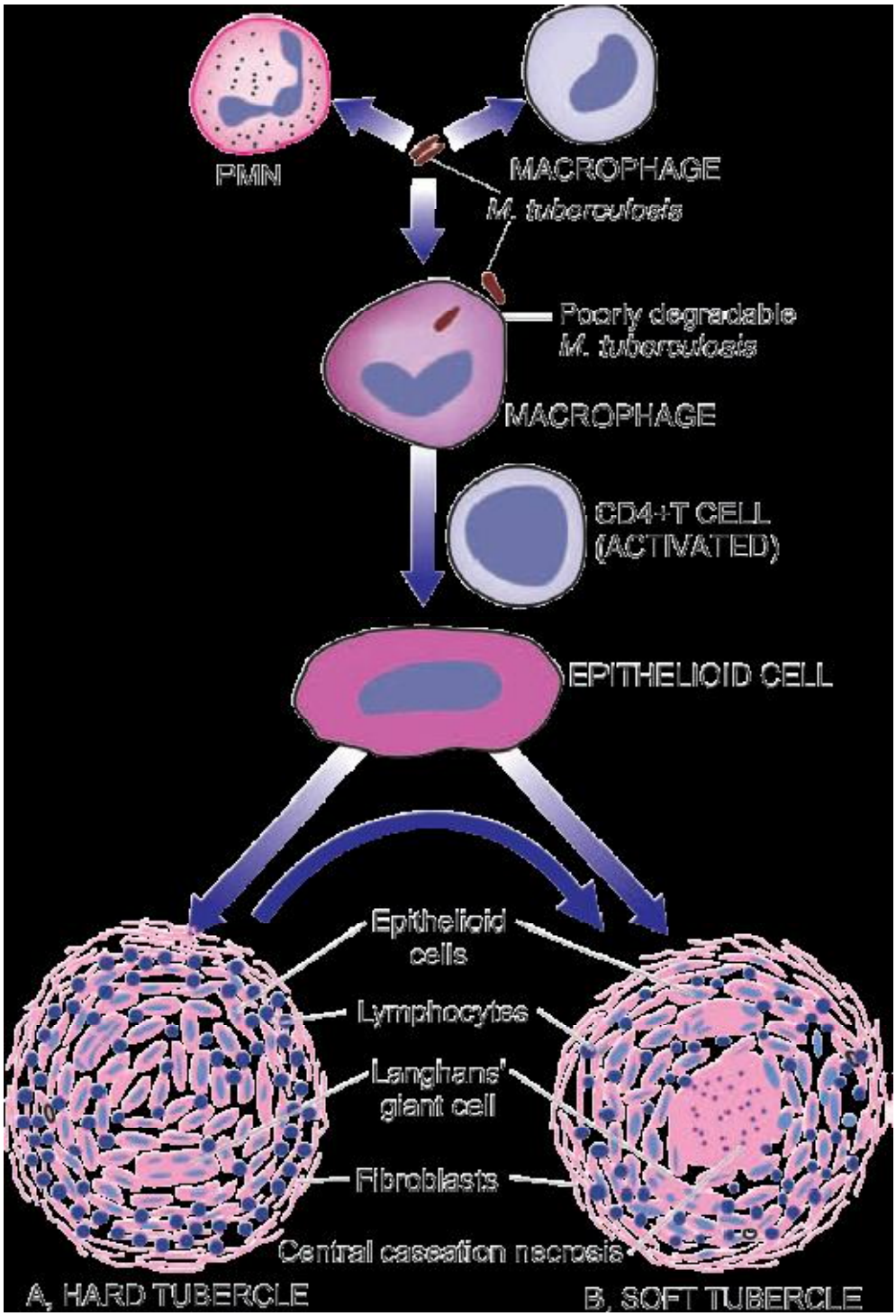
1. When the tubercle bacilli are injected intravenously in to the guinea pig, the bacilli are lodged in pulmonary capillaries where an *initial response of neutrophils* is evoked which are rapidly destroyed by the organisms.
2. After about 12 hours, there is *progressive infiltration by macrophages.* This is due to coating of tubercle bacilli with serum complement factors C2a and C3b which act as opsonins and attract the macrophages. Macrophages dominate the picture throughout the remaining life of the lesions. If the tubercle bacilli are, however, inhaled into the lung alveoli, macrophages predominate the picture from the beginning.
3. The macrophages start *phagocytosing* the tubercle bacilli and either kill the bacteria or die away themselves. In the latter case, they further proliferate locally as well as there is increased recruitment of macrophages from blood monocytes.
4. As a part of body's immune response, T and B cells are activated. Activated CD4+T cells develop the cell-mediated *delayed type hypersensitivity reaction*, while B cells result in formation of antibodies which play no role in body's defence against tubercle bacilli.

5. In 2-3 days, the macrophages undergo structural changes as a result of immune mechanisms-the cytoplasm becomes pale and eosinophilic and their nuclei become elongated and vesicular. These modified macrophages resemble epithelial cells and are called *epithelioid cells*.
6. The epithelioid cells in time aggregate into tight clusters or *granulomas*. Release of cytokines in response to sensitized CD4+T cells and some constituents of mycobacterial cell wall play a role in formation of granuloma.
7. Some of the macrophages form *multinucleated giant cells* by fusion of adjacent cells. The giant cells may be Langhans' type having peripherally arranged nuclei in the form of horseshoe or ring, or clustered at the two poles of the giant cell; or they may be foreign body type having centrally-placed nuclei.
8. Around the mass of epithelioid cells and giant cells is a zone of lymphocytes, plasma cells and fibroblasts. The lesion at this stage is called *hard tubercle* due to absence of central necrosis.
9. Within 10-14 days, the centre of the cellular mass begins to undergo caseation necrosis, characterised by cheesy appearance and high lipid content. This stage is called *soft tubercle* which is the hallmark of tuberculous lesions.

The development of caseation necrosis is possibly due to interaction of mycobacteria with activated T cells (CD4+ helper T cells via IFN-γ and CD8+ suppressor T cells directly) as well as by direct toxicity of mycobacteria on macrophages.

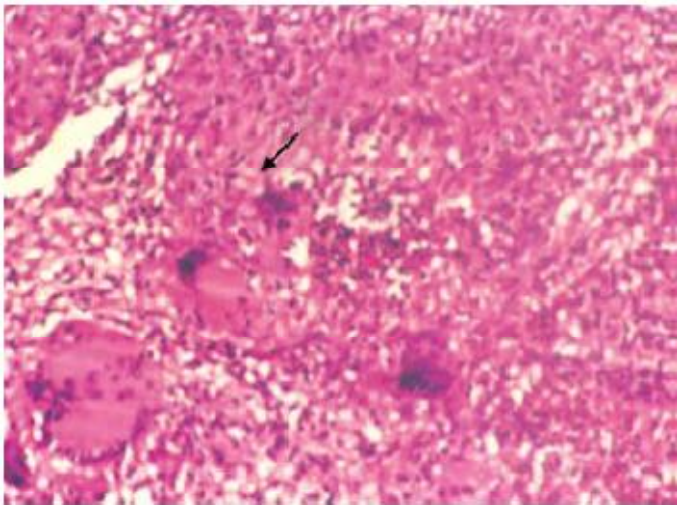
*Microscopically***,** caseation necrosis is structureless, eosinophilic and granular material with nuclear debris.

10. The soft tubercle which is a fully-developed granuloma with caseous centre does not favour rapid proliferation of tubercle bacilli. *Acid-fast bacilli* are difficult to find in these lesions and may be demonstrated at the margins of recent necrotic foci and in the walls of the cavities.


PMN
MACROPHAGE
M. tuberculosis
Poorly degradable
M. tuberculosis
MACROPHAGE
CD4+T CELL
(ACTIVATED)
EPITHELIOID CELL
Epithelioid
cells
Lymphocytes
Langhans'
giant cell
Fibroblasts
Central caseation necrosis
A, HARD TUBERCLE
B, SOFT TUBERCLE

THE FATE OF A GRANULOMA IS VARIABLE:

1. The caseous material may undergo liquefaction and extend into surrounding soft tissues, discharging the contents on the surface. This is called *cold abscess* although there are no pus cells in it.
2. In tuberculosis of tissues like bones, joints, lymph nodes and epididymis, sinuses are formed and the *sinus tracts* are lined by tuberculous granulation tissue.
3. The adjacent granulomas may *coalesce* together enlarging the lesion which is surrounded by progressive fibrosis.
4. In the granuloma enclosed by fibrous tissue, calcium salts may get deposited in the caseous material *(dystrophic calcification)* and sometimes the lesion may even get ossified over the years.



CLINICAL FEATURES OF INTRA OCULAR TUBERCULOSIS

Any ocular tissue may be affected, including the ocular adnexa, the cornea, the sclera, the Uveal tract, the retina, and the optic nerve.[11] Of the various manifestations of ocular TB, the most common clinical presentation appears to be posterior Uveitis, followed by anterior Uveitis, pan Uveitis, and intermediate Uveitis.

The clinical features of any Uveitic eye are described by the criteria given by SUN working group.

"TABLE 1- SUN Working group Anatomical Classification Of Uveitis

Type	Primary site of inflammation	includes
Anterior Uveitis	Anterior chamber	Iritis, iridocyclitis, anterior cyclitis
Intermediate Uveitis	vitreous	Pars planitis, posterior cyclitis, and hyalitis
Posterior Uveitis	Retina or choroid	focal or multifocal or diffuse choroiditis, chorioretintis , retinochoroiditis, retinitis and neuroretinitis
Pan Uveitis	Anterior chamber, vitreous, retina and choroid"	

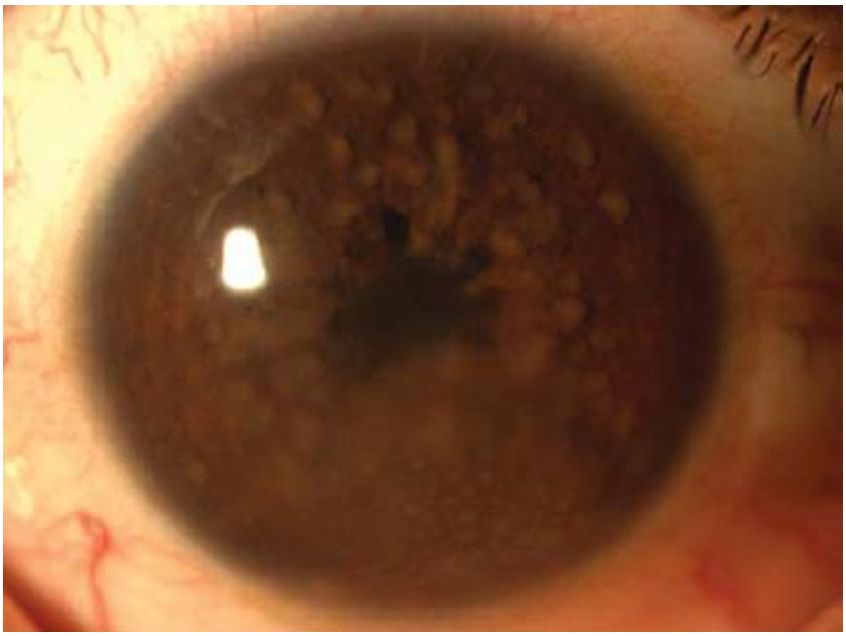
The clinical features of intraocular tuberculosis is well described by gupta et al.[5]

"Table 2 – clinical presentation of intraocular tuberculosis

1	Anterior uveitis	Granulomatous, non granulomatous iris nodules ciliary body tuberculoma
2	Intermediate uveitis	Granulomatous Non granulomatous With organizing exudates in pars plana/peripheral uvea
3	Posterior and panuveitis	Choroid tubercle Choroid tuberculoma Subretinal abscess Serpiginous like choroidtis
4	Retinitis and retinal vasculitis	
5	Neuroretinitis and optic neuropathy	
6	Endophthalmitis and panophthalmitis"	

1. ANTERIOR UVEITIS

Tuberculosis can cause acute or chronic granulomatous anterior Uveitis which may present with iris or angle granulomas with mutton-fat keratic precipitates and posterior synechiae. There may be mild or moderate recurrent iridocyclitis along with complicated cataract and possibly vitritis. [5]



The clinical features of anterior Uveitis is described by the criteria given by SUN working group.[21]

“TABLE 3- SUN working group grading scheme for anterior chamber cells

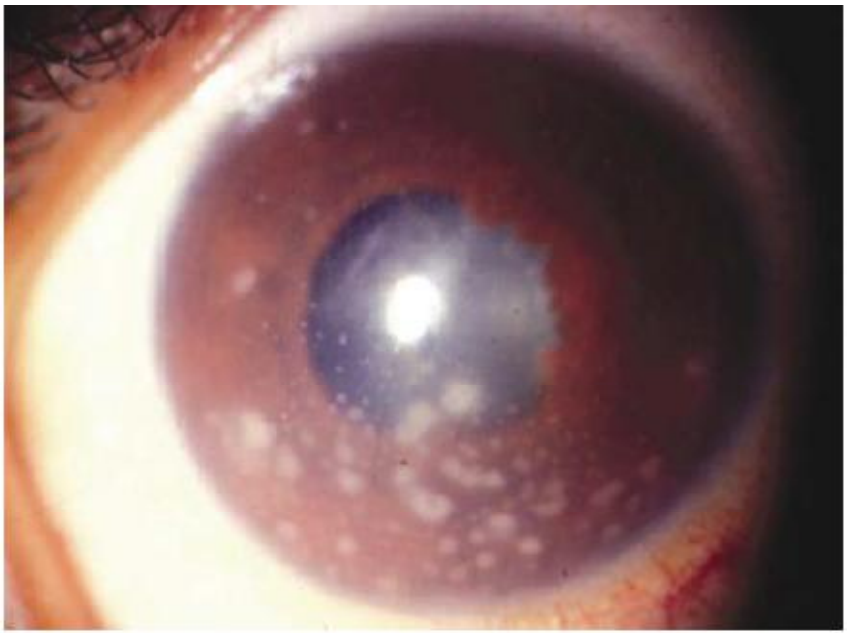
GRADE	CELLS/FIELD
0	<1
0.5	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Field size is 1mm by 1mm slit beam”

“TABLE 4- SUN working group grading scheme for anterior chamber flare

GRADE	DESCRIPTION
0	none
1+	faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrinous or plastic aqueous)

Field size is 1mm by 1mm slit beam”

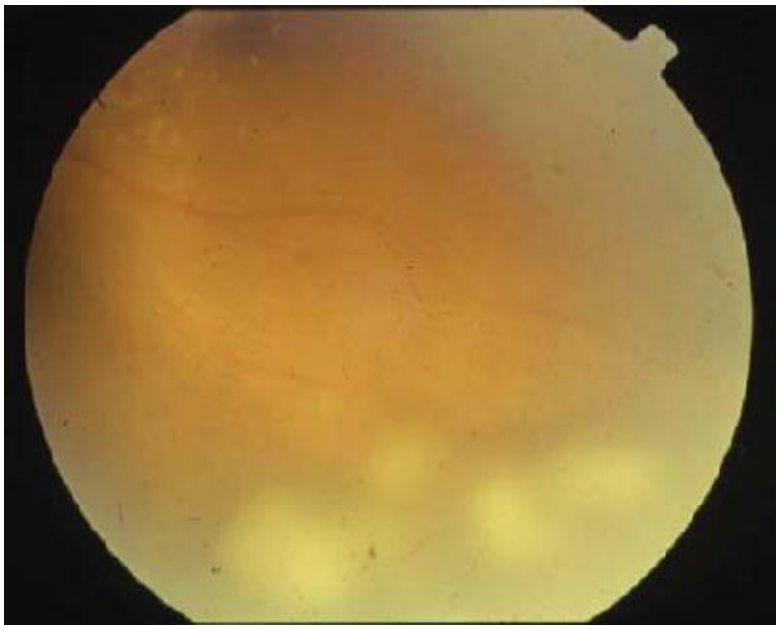


Mutton fat granulomatous KPs

2. Intermediate Uveitis

The common manifestation of intermediate Uveitis in intraocular tuberculosis is pars planitis. Patients generally present with following:

- with a low– grade smoldering chronic Uveitis
- vitritis
- snow ball opacities
- snow banking
- vascular sheathing in periphery
- retinochoroidal granuloma.[5]



Snow ball opacities

The grading of vitritis can be done according to the recommendations given by the 'National Eye Institute system' for grading vitreous haze.

"Table 5 Grading of Vitreous Haze through the binocular indirect ophthalmoscope (BIO SCORE)

SCORE	DESCRIPTION	CLINICAL FINDING
0	nil	none
0.5	trace	Occasional cells
1	minimal	Posterior pole clearly visible
2	mild	Posterior pole details slightly haze
3	moderate	Posterior pole details very haze
4	marked	Posterior pole details barely visible
5	severe	Fundus details not visible"

3. POSTERIOR AND PAN UVEITIS

In tuberculous posterior Uveitis, the ocular manifestations include :

1. Choroidal tubercles
2. Choroidal tuberculoma
3. Subretinal abscess and
4. Serpiginous like choroiditis

a. Choroidal Tubercles

Most common intraocular manifestation of tubercular posterior Uveitis is multiple choroid tubercles .It occurs from hematogenous spread of the tubercular bacilli. Tuberculoma results occasionally from a tubercle that may continue to grow in to a solitary mass.

Picture showing choroidal lesion along superotemporal arcade and healed chorioretinal scars inferiorly.

b. Choroidal Tuberculoma

Intraocular tuberculosis may present as a large tuberculoma. [5]

Various locations of tuberculoma - anywhere in the choroid, in the macula, the equator, posterior pole or in a juxtapapillary location.

The tuberculomas generally present as a large solitary mass and may mimic a tumor.

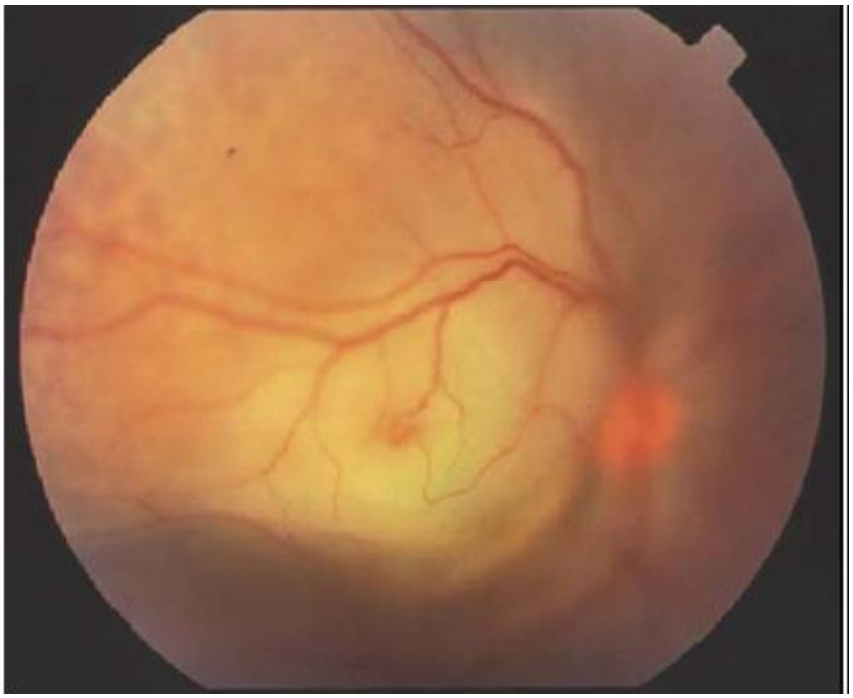
c. Subretinal abscess

Multiplication of the bacilli in the granulomas

↓

Liquefaction necrosis and abscess formation.

Gupta v et al has reported “these abscesses are more yellowish in color indicating liquefaction necrosis , have overlying retinal hemorrhages and have a tendency to develop retinal angiomatous proliferation over a period of time. These lesions usually heal with ATT and healed lesions may show pigmentation and atrophy with chances of good visual recovery”.[5]



d. Serpiginous-like choroidtis

Serpiginous choroiditis or otherwise known as geographic helicoids peripapillary choroidopathy is defined as " a chronic ,recurrent inflammation that primarily involves the choroid and choriocapillaries and progresses to involve the retina secondarily".[5] A relentless progression is common in tuberculous serpiginous like choroiditis lesions .

4. Retnitis and Retinal vasculitis

Patients with ocular tuberculosis can have vasculitis that may involve veins or rarely the arteries, and there may be associated systemic disease.[5] verhoff and simpson reported "a tubercle within the central retinal vein in an eye enucleated for neovascular glaucoma" . knox stated "periphlebitis was a common presentation of intra ocular tuberculosis , second only to chronic iridocyclitis.[5]whether the vasculitis per se is infective or whether it represents a hypersensitivity response to M.tuberculosis remains speculative".

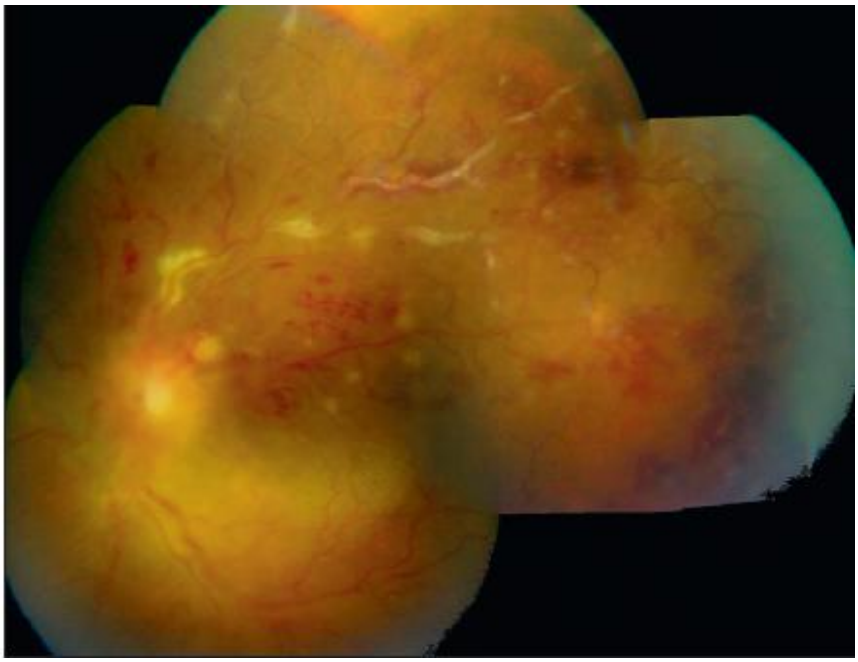
Organism in ocular tissue

↓

Immune hypersensitivity response

↓

vasculitis



b. Eales Disease

There are recent reports suggesting association of tuberculosis with Eales disease due to demonstration of TB bacilli in vitreous samples from patients with Eales disease.

Eales disease is usually peripheral, invariably bilateral retinal vasculitis resulting in peripheral non-perfusion and neovascularization in young male population. Patients present with painless vision loss of varying degrees, usually due to vitreous hemorrhage, and rarely due to retinal ischemia.

The various stages of Eales disease are:

1. Stage of inflammation
2. Stage of ischemia
3. Stage of neovascularization
4. Stage of sequelae

5. Neuroretinitis and Optic neuropathy

Tuberculous optic neuropathy is either due to - direct infection or a hypersensitivity reaction to tuberculous bacilli.[22] The involvement of the nerve may manifest as an optic nerve tubercle , papillitis , papilledema , optic neuritis, retrobulbar neuritis, neuroretinits , or optic chiasmatic arachnoiditis.[5]

6. Endophthalmitis and Panophthalmitis

INVESTIGATIONS FOR OCULAR TUBERCULOSIS

1. Ocular imaging studies in intraocular tuberculosis

1. Fluroscein angiography

On angiography in case of choroidal tubercles there is hypofluorescence during dye transit followed by hyperfluorescence in later stages. Inactive lesions may show hyperfluorescence during dye transmission. large choroidal granulomas show early hyperfluorescence and pooling of dye during the late phase.

In diffuse serpiginous like choroiditis - fluorescein angiography shows an initial hypofluorescent active edge and diffuse staining of the active advancing edge.[5]

A. Choroidal tubercle near macula
B. Fundus fluoresecein angiography showing - vascular staining and perivascular leakage over the lesion suggesting active retinitis
C. Fundus fluorescein angiography showing - well demarcated choroidal tubercle with hyper fluorescence and pooling of dye.

2 .Indocyanine green angiography

Subclinical choroidal lesions can be detected in Indocyanine green angiography which are seen as early & intermediate hypofluorescent spots and iso or hyperfluorescent during the late phases . Since ICG changes are reversible , they can be used to monitor response to theraphy.[5]

3. Optical coherence tomography:

With a relatively clear media, OCT can help detect retinal pathologies such as subretinal neovascular membrane and CME.

4.Ultrasonography

Ultrasonography is useful for differentiating retinoblastoma , malignant melanoma & metastatic tumors from tuberculomas.

5.Ultrasound Biomicroscopy

UBM is used to detect granuloma in the parsplana region.

2. Systemic investigations

1. Purified Protein Derivative /Mantoux skin test and Its Interpretation:

- done because ocular hypersensitivity is related to cutaneous hypersensitivity
- done by giving intradermal injection of 5 TU of purified protein derivative to raise a wheal of 6- 10 mm.
- result is read by measuring induration at the site of injection at 48-72 hrs.

INDURATION MEASUREMENT	RESULT	SPECIAL CONSIDERATION
Less than 5 mm	negative	nil
5- 10 mm	positive	If patient is HIV positive or if patient Has healed tuberculous lesions In chest radiograph
More than 10 mm	positive	If patient resides in high incidence areas or patient lives in high risk settings
15 mm	positive	

FALSE NEGATIVE:

1. Severe tuberculous infection
2. Moribund patient

FALSE POSITIVE:

Vaccination with BCG

2. Chest Radiography and Computerized Tomography

Active or healed /primary or reactivated pulmonary tuberculosis can be made out with chest radiograph. chest x-ray can provide evidence of tuberculosis. Unilateral or bilateral Hilar or paratracheal lymph node enlargement is quite characteristic of primary tuberculosis. Inactive disease is characterized by Calcified hilar lymph nodes or pulmonary nodules . Computerized tomography of the chest and skeleton and cerebral MRI are more sensitive than radiograph.

3.Serodiagnosis

Serodiagnostics tests have low sensitivity and high false positive rates & hence not preferred currently.

4. Interferon–g release assays(IGRA)

This test measures interferon-gamma released by sensitized T cells after stimulation by M.tuberculosis antigens.[5]The newer versions of the test use antigens that are very specific to M.tuberculosis and include - early secreted antigen test (ESAT) 6, culture filtrate protein (CFP)-10. The newer antigens are more specific are not shared with BCG vaccine strains or other species of Mycobacterium .Two kits are available commercially –

1. T-SPOT.TB test (Oxford immunotec Ltd,Oxford,UK)
2. Quantiferon – TB GOLD (Carnegie,Australia).

Doycheva D et al concluded that " In quantiferon positive patients with severe Uveitis forms such as serpiginous choroiditis and occlusive retinal vasculitis, 18 F-FDG-PET/CT 18(F-fluorodeoxyglucose positron emission tomography /CT) is useful to identify lesions appropriate for biopsy and helps to establish the diagnosis and appropriate therapy for presumed tuberculosis-induced intraocular inflammation".[10]

Ang m et al in a prospective cohort study stated that " the interferon gamma release assay (IFN-c)(IGRAs) can be used as diagnostic test for

tuberculosis (TB)-associated Uveitis in combination with clinical signs and TST to diagnose TAU".[9]

5.Xpert MTB/RIF(a new rapid molecular test)

WHO TB report 2013 Xpert MTB/RIF states that, " a rapid molecular diagnostic test , is being rapidly adopted by countries to detect TB and rifampicin –resistant TB. By end of june 2013,1402 testing machines and 3.2 million test cartridges had been procured by 88 of the 145 countries eligible for concessional prices".

3.Direct evidence from ocular tissues:

1. Examination of smear and staining for Acid-Fast organisms

Direct microscopy of the smears is not often helpful in the diagnosis of intraocular tuberculosis since the yield of organisms from intraocular fluids is low. In cases with ceseation necrosis and endophthalmitis which might yield more bacilli, examinations of stained smears from these eyes may help establish the diagnosis.

2.Culture of intraocular fluid/tissue:

Culture media: Lowenstein –Jensen medium

Duration : 8 weeks

Staining : ziehl-neelson stain

Drawbacks: .

1. The process is prolonged and cumbersome
2. May not provide positive results because of the low yield of organisms from the intraocular fluids.

3.Polymerase Chain Reaction:

This is especially useful for intraocular fluids, because PCR can amplify mycobacterial DNA several –fold for easy detection and hence can be performed with very small sample sizes. Samples can be - aqueous ,vitreous humor, subretinal fluid, or rarely, tissue obtained by chorioretinal biopsy. [5]The reported PCR-positivity for M.tuberculosis is 33% of cases in retinal vasculitis and 66% in granulomatous panuveitis. Wroblewosky at al in a restropective case series suggested that in dealing with those populations at increased risk

of tuberculosis or patients receiving biologic therapy ,these tests are recommended.

DIAGNOSIS OF INTRAOCULAR TUBERCULOSIS

There is no well defined criteria for diagnosis of intraocular tuberculosis. Based on clinical parameters , follow-up examinations, Therapeutic response to ATT and laboratory investigations like PCR analysis of intraocular fluid, culture or other bacteriological examination of ocular fluids, Gupta et al proposed the following guidelines for the diagnosis of intraocular tuberculosis. “Taken broadly , these diagnostic criteria enable the clinician to determine when to initiate ATT. All the criteria are broadly described under five sections as described below.

Section 1 Clinical signs

All signs mentioned in table 2 page 16

Section 2 Ocular investigation

A. Demonstration of AFB by microscope or culture of M.tuberculosis from the ocular fluids.
B. Positive polymerase chain reaction from ocular fluids for IS 6110 or other conserved sequences in M.tuberculosis genome.

Section 3 systemic investigations

1. positive mantoux test
2. evidence of healed or active tubercular lesion on radiography of chest.
3. evidence of confirmed active extrapulmonary tuberculosis either by microscopic examination or by culture of the affected tissue for M.tuberculosis

section 4 exclusion of other Uveitis entities

In the geographic regions where tuberculosis is low in incidence, other causes of Uveitis must be excluded by various laboratory investigations including serology for syphilis , toxoplasmosis and others.

Section 5 therapeutic test

A positive response to 4 drug ATT over a period of 4 to 6 weeks. Therapeutic trial with single drug isoniazid should be avoided due to risk of development of resistence. It is important to refer such a patient to a TB expert who can initiate and monitor the treatment. The therapeutic response to ATT in the eye should however be evaluated by the ophthalmologist.

Any one or more of the clinical signs listed under subsequent section 1 in combination with any of the positive tests under section 2 could be considered a confirmed case of intraocular tuberculosis. Any one or more of the clinical signs listed under section 3 or a positive therapeutic trial section 5 in combination with 4 could be considered presumed ocular tuberculosis and referred to a TB specialist to initiate a full course of ATT."

TREATMENT

Recommended therapy for tuberculosis Uveitis consists of - isoniazid 5mg/kg/d, rifampicin 450 mg/d if body weight is <50 kg and 600 mg if the weight is greater than 50 kg, ethambutol 15 mg/kg , and pyrazinamide 25 to 30 mg/kg/d initially for 2 months. Thereafter, rifampicin and isoniazid are used for at least another 4 to 7 months.[12] oral prednisolone is added at a dose of 1mg/kg/d until a clinical response is seen then a slow reduction is established.[5]

Abu El et al studied 51 patients with presumed tuberculous Uveitis treated with ATT and systemic corticosteroids & reported that, " all eyes showed resolution of inflammation without any recurrence after stopping antituberculous therapy and systemic corticosteroids. Previous studies reported a favorable response to antituberculous therapy when administered concomitantly with systemic corticosteroids in a patients with presumed tuberculosis Uveitis.[5] The management of active retinal vasculitis requires the use of systemic corticosteroids and appropriate anti tuberculous therapy. New vessel formation associated with retinal vasculitis and capillary closure responds to panretinal photocoagulation. Early vitrectomy and adequate endolaser photocoagulation should be considered in eyes with nonresolving vitreous hemorrhage associated with active fibrovascular proliferation".

However no clinical trials exists on the efficacy of topical or systemic steroids in ocular tuberculosis .[7] we will be treating with lower dose of steroids than usual prescribed dose (1mg/kg body wt/day) based on our clinical experience, to see the reduced steroid related toxicity with similar therapeutic benefit (except for lesions near macula or optic disc, which will be treated with the usual prescribed dose i.e., 1mg/kg body wt/day).

PHARMACOLOGY OF ETHAMBUTOL

Ethambutol is selectively tuberculostatic and clinically as active as streptomycin. Fast multiplying bacilli are more susceptible as are many atypical mycobacteria. Added to the triple drug regimen of RHZ it has been found to hasten the rate of sputum conversion and to prevent development of resistance.

The mechanism of action of Ethambutol is not fully understood, but it has been found to inhibit arabinosyl transferases involved in arabinogalactan synthesis and to interfere with mycolic acid incorporation in mycobacterial cell wall.

Resistance to Ethambutol develops slowly; in many cases it is due to alteration in the drug target gene. No cross resistance with any other antitubercular drug.

About ¾ of an oral of Ethambutol is absorbed. It is distributed widely but penetrates meninges incompletely and is temporarily stored in RBCs. Less than ½ of Ethambutol is metabolized. It is excreted in urine by glomerular filtration and tubular secretion; plasma t1/2 is 4 hrs.caution is required in its use in patients with renal disease.

The most important ocular side effect of ethambutol is toxic optic neuropathy. Ethambutol produces few other symptoms such as nausea,rashes, fever, neurological changes are infrequent. Hyperuricemia is due to interference with urate excretion.

TOXIC OPTIC NEUROPATHY

Toxic optic neuropathies can present as an acute or chronic damage that may result from an acute or sustained exposure to the noxious substance. Although these resemble closely the pattern of the involvement that may occur from a nutritional deficiency closely, in some cases, it can present with an acute onset disk edema with marked visual loss (as in case of methyl alcohol poisoning).

The various agents that can cause toxic optic neuropathy are:

Amiadarone	Aspidium
Arsenicals	Ethambutol
Carbon disulfide	Ethylene Glycol
Dinitrobenzene	Hexachlorophene
Disulfiram	Iodoform
Haloquinols	Isoniazid
Intetrix	Methanol
Iodoquinol	Penicillamine
Lead	Plasmocid
Pheniprazine	Tobacco
Quinine	Thallium

The list is exhaustive but nevertheless incomplete, and many new drugs are likely to be reported causing toxic neuropathies over a period of time. However, it is difficult to establish a direct cause-and-affect relationship in most cases. At the same time, knowing the cause of toxic neuropathy is the cornerstone in the treatment of the condition and may have far reaching medical and legal implications.

Discontinuation of the exposure is the cornerstone in the treatment of the condition and in conditions for which a specific treatment exists, an accurate etiological diagnosis is essential.

PATHOPHYSIOLOGY

The etiology is multifactorial.

C. Impairment of vascular supply or metabolism by toxins
D. In patients who abuse tobacco and alcohol - malnutrition is the principal cause of the visual loss.

The specific deficiencies in vitamins proteins with

sulfur- containing amino acids, or combination of both

Accumulation of formic acid

Formic acid and cyanide disrupts ATP production

Impairment of ATP- dependent axonal transport

Optic neuropathy

It has been hypothesized that the chelating properties of ethambutol contribute to its neurotoxicity, but this has yet to be proven. The mechanism of the neurotoxicity that occurs from the antiarrhythmic amiodarone remains unclear. Researchers believe that it may relate to a lipidosis that is induced by the drug.[23]

APPROACH TO PATIENT WITH SUSPECTED TOXIC OPTIC NEUROPATHY

1. Possibility of inflammatory lesions and malignancies by appropriate investigations, visual fields, visual evoked potentials and neuroimaging should be ruled out. It may be advisable to consider a neuroimaging, preferably MRI in all cases.
2. Complete blood count with indices, standard blood chemistries, protein electrophoresis, and folate levels should be evaluated.
3. If all the above findings are normal, an ERG may be considered to exclude cone-rod dystrophy, which can manifest with optic disk pallor and central scotomas.
4. If ERG is normal, serological tests for Leber's hereditary optic neuropathy mutation and a 24-hour urine collection to rule out lead and thallium poisoning may be considered.
5. If all these test are negative, or if there is a specific deficiency of nutrients as picked up by the blood tests, treatment with thiamine, 50 mg/day, multivitamins, and possibly cyanocobalamin should be done. Patients should be encouraged to stop tobacco smoking and limit alcohol consumption.

HISTORY:

Should include :

1. Diet history
2. History of exposure to toxins/drug
3. Personal history (smoking/ drinking alcohol)
4. Occupational history (exposure to occupational toxins)
5. History of chronic disease or illness
6. Family history

SIGNS AND SYMPTOMS*:*

1. Bilateral painless progressive defective vision
2. Decreased color vision
3. Decreased contrast sensitivity
4. Centrocaecal scotoma
5. Optic disc pallor involving the temporal quadrant.
6. No rapd
7. Pupils : bilateral sluggish reaction to light
8. Disc hyperemia and edema in few acute intoxications
9. In ethambutol toxicity – fundus normal initially, later atrophy develops
10. In isoniazid toxicity – optic disc swelling is seen

11. In Amiodarone Toxicity – Bilateral Disc Swellimg With Flame Shaped Hemorrhage

Investigations

Evaluation for toxic optic neuropathy includes a complete ocular examination including color vision, contrast sensitivity and visual fields.

Visual field testing and color vision testing absolutely essential in the evaluation of any patient suspected of having toxic optic neuropathy. Central or cecocentral scotomata with preservation of the peripheral field are characteristic visual field defects. These cases show red green colour defects, but sometimes blue yellow defects may also be seen.

COLOR VISION :

Colour sense is the ability of the eye to discriminate between colours excited by light of different wavelengths.

THEORIES OF COLOR VISION

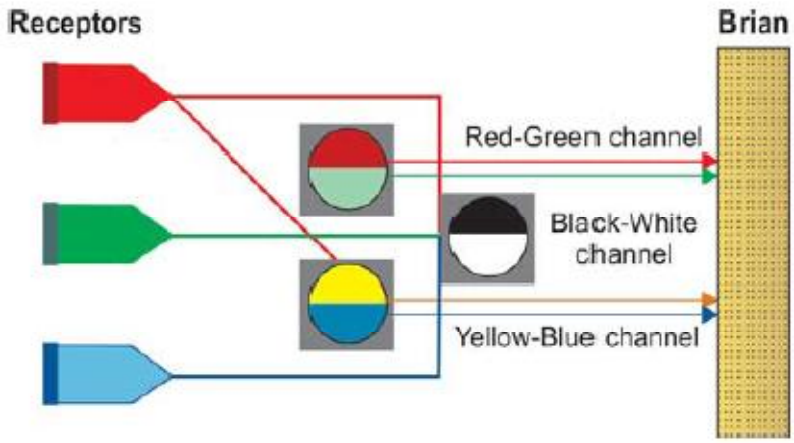
Trichromatic theory—Young-Helmholtz (1802) proposed " that color vision depends on the three different sets of retinal fibers responsible for perception of red, green, and violet".

Opponent theory—Hering (1878) proposed that "yellow-blue and red-green represent opponent signals producing four color primaries red, green, yellow,

and blue and not just three". Whiteblack opponency proposed by him has been abandoned in most modern versions of the theory.

Zone theory—Donder (1881) proposed that " the Trichromatic theory operates at the receptor level and the Opponent theory applies to the subsequent neural level of color vision processing. This is the basis of modern color vision theory. At the receptor level vision is trichromatic (based on the perception of three primary colors) and requires three types of cone photopigment. Each photopigment absorbs particular wavelengths of light in the short (blue, 440 nm), middle (green,545 nm), or long (red, 560 nm) wavelength region of the visible spectrum. These cones are the basic mediators of color vision.

If one or more of their pigments is missing, color blindness results".[24]



COLOUR VISION TESTS:

Pseudoisochromatic Plate

- Ishihara Plates
- Standard Pseudoisochromatic Plates
- Color Vision Testing Made Easy (CVTME)
- City University test
- American Optical Hardy-Rand-Rittler Plates

Ishihara Charts

This test is based on the principle of confusion of the pigment color in red-green color defectives. This is an easy and rapid test used most commonly for screening purposes. Ishihara charts are available in 14, 24 or 38 plates. The 10th edition of Ishihara has 38 plates. Five different design formats are used in 38 plates Ishihara.[24]

Interpretation*:*

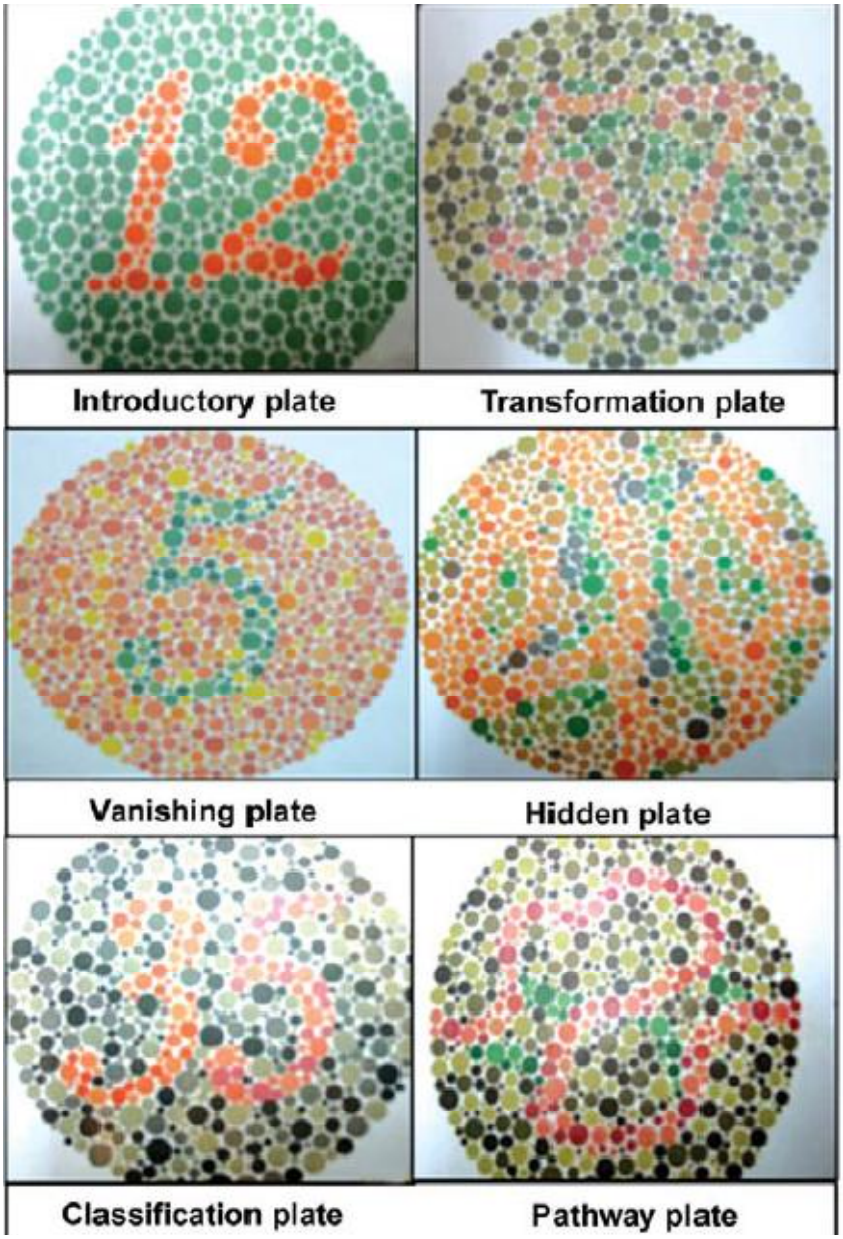
The number of plates of each sub-type varies with the edition. For the 38-plate edition, plates 1 to 21 are for screening red-green defects, and plates 22 to 25 are for differential diagnosis of protans and deutans. The plates are designed to be appreciated correctly in a room which is lit adequately by daylight. The plates are held at a distance of 75 cm perpendicular to the line of sight.

Out of 21 plates, if 17 or more plates are read correctly by an individual his color sense should be regarded as normal. If 13 or less plates are correctly read then the person has a red-green color defect.9 Disadvantage of this test is that it neither tests for tritanope

nor grades the degree of deficiency.

American Optical Hardy- Rand-Ritter (HRR) is the test of choice for quantitative diagnosis and the Standard Pseudoisochromatic Plates Part for acquired color deficiency.[24]

ISHIHARA PLATES



HARDY – RAND- RITTLER :

1. It is a pseudo isochromatic chart test.
2. Useful to identify protan, deutran, tritan defects.
3. Consists of 24 plates with vanishing designs containing geometric shapes. 4 plates are introducing plates, 6 are for screening, 10 are for grading severity of protan and deutran defect and last 4 for grading tritan defect.

THE LANTERN TEST :

The subject has to name various colours shown to him using lantern.

There are three types:

1. EDRIGE GREEN
2. HOLMES WRIGHT TYPE A
3. HOLMES WRIGHT TYPE B

FARNSWORTH MUNSELL 100 HUE TEST :

It is a spectrographic test where the colored chips are arranged in ascending order.

CITY UNIVERSITY COLOR VISION TEST:

It is also spectrographic test.

Here, colored plates are matched to closest hue from 4 sorrounding color plates.

NAGELS ANOMALOSCOPE TEST :

The observer is asked to mix red and green color in a proportion to match the given yellow color hue.

It detects red-green deficiency

HOLMES' WOOL TEST :

The subject is asked to make a series of color matches from a selection of colored wools.

CENTRAL FIELDS TESTING

TANGENT SCREEN

The tangent screen may be used at a distance of one or two meters, and should be able to test central 30^{o} of the patient's visual fileds.

An uniform illumination of 7 foot candles is preferred Visual fields could be tested kinetically by moving the stimulus from periphery towards fixation .visual fields can also be tested statically with test objects shown intermittently.

Fixation can be tested repeatedly by concealing and exposing the test objects in the blind spot area. Fixation has obviously shifted , if the patient can see the object in the blind spot area.

Thus, the Bjerrum screen can provide more detailed, quantitative visual field information than that afforded by confrontation visual field testing. It may

even provide information that is equal to or better than those provided by the automated perimeters, in the hands of a skilled perimetrist.[21]

CONTRAST SENSITIVITY:

Contrast sensitivity is the ability to perceive slight changes in luminance between regions that are not separated by definite borders and is just as important as the ability to perceive sharp outlines of relatively small objects. It is only the latter ability that is tested by means of the snellen's test types.Further , contrast sensitivity may be impaired even in the presence of normal visual acuity.[22]

TYPES OF CONTRAST SENSITIVITY:

1. SPATIAL CONTRAST SENSITIVITY:

Spatial contrast sensitivity refers to detection of striped pattern at various levels of contrast and spatial frequencies. In its measurement, patient is presented with sine wave gratings of parallel light and dark bands and is asked to tell the minimum contrast at which the bars can be seen at each frequency. The width of the bars is defined as spatial frequency which expresses the number of pairs of dark and light bars subtending an angle of 1 degree at the eye. A high spatial frequency implies narrow bars, whereas low spatial frequency indicate wide bars.[22]

2. TEMPORAL CONTRAST SENSITIVITY:

Here the contrast sensitivity function is generated for time related processing in the visual system by presenting a uniform target field modulated sinusoidal in time, rather than as a function of spatial position.

Both temporal and spatial contrast sensitivity testing yield significantly more complete and systematic data on the status of visual performance than the conventional tests.

MEASUREMENT OF CONTRAST SENSITIVITY:

When a subject is presented with the grating frequencies and contrast below which resolution is impossible, it indicates the threshold level; and the reciprocal of this contrast threshold gives the contrast sensitivity.

Contrast sensitivity is measured as (Lmax – Lmin)/(Lmax+ Lmin), where L is the luminance recorded by photocells scanning across the gratings.

METHODS OF MEASUREMENT:

Various methods have been developed to measure contrast sensitivity. Boldis wollner introducing contrast sensitivity measurement in clinical practice, suggested the name visugram , analogue to an audiogram , to describe a patient's 'contrast sensitivity curve'.

The deficits were expressed in terms of decibels , and three types of deficits were described:

1. High –frequency type characterized by increasing loss at high frequency
2. A level-loss type characterized by a similar loss for all spatial frequencies.
3. A selective loss type characterized by deficits of spatial frequencies in a narrow band

   In general, the methods recommended to measure contrast sensitivity include:

   Simple plates, cathode ray tube display on a screen, letter acuity charts, laser interferometer which produces grating on retina, visual field testing using low contrast rings on stimuli , pattern discrimination test , proto type for forced choice printed test, visually evoked cortical potentials to checkerboard pattern reversal dependent contrast threshold measurement , two alternative forced choice test and many more.[22]

   Some of the simple, inexpensive but reliable methods of measuring contrast sensitivity are described in belief in the following text

1. ARDEN GRATINGS:

Arden in 1978 introduced a booklet containing seven plates: one screening plate and six diagnostic plates.

The contrast changes from top to bottom and covers a range of approximately 1.76 log units. The plates are studied at 57 cm with spatial frequency increasing from 0.2 cycles /degree to 6.4 cycles/degree , each being double the frequency of the previous one. A score of 1-20 is assigned to each plate depending upon the amount of plate uncovered. Sum of six plates with an upper limit of 82 was established for normal subjects together with an intraocular difference of less than 12.[22]

2. CAMBRIDGE LOW- CONTRAST GRATINGS:

Cambridge low-contrast gratings consist of a set of ten plates containing gratings in a spiral bound booklet. To perform the test the booklet is hung on a wall at a distance of 6 m. the pages are presented in pairs, one above the other.

One page in each pair contains gratings and the other is blank but the pages have the same mean reflectance. The subject is simply required to choose which page, top or bottom, contains the gratings. The pages are shown in order of descending contrast and are stopped when the first error is made.

Depending upon the total score of a patient from four series, the contrast sensitivity is noted from the conversion table.

3. PELLI – ROBSON CONTRAST SENSITVITY CHART

This chart consists of letters that subtend an angle of 3 degree at a distance of 1m. The chart is printed on both sides. The two sides have different letter sequence but are otherwise identical. The letters on a chart are organized as triplets , there being two triplets in each line. The contrast decreases from one triplet to the next. The log contrast sensitivity varies from 0.00 to 2.25.

To perform the test, the chart is hung on the wall, so that its centre is approximately at the level of the subject's eye. The chart is illuminated as uniformly as possible, so that the luminance of the white areas is between the acceptable range 60 and 120 cd/m which corresponds to a photographic exposure between 1/15 and 1/30 second at f/5.6 with ASA of 100. The luminance is determined with the help of light meter.

While recording, the subject sits directly in front of the chart at a distance of 1m (with best distance correction). The subject is made to name or outline each letter on chart starting from the upper left corner and reading horizontally across the line. Subject is made to guess even when he or she believes that the letters are invisible. The test is concluded when the subject guesses two of the three letters of the triplet incorrectly. The subject's sensitivity is indicated by the finest triplet for which two of the three letters are named correctly. [25]

4. VISTECH CHART :

This chart consists of sine wave gratings and is used at a distance of 3 m from the subject. In the test, contrast is assessed at several spatial frequencies and the subject has to identify orientation of grating, i.e., whether vertical or 15 degree clockwise or anticlockwise.[22]

FACTORS AFFECTING CONTRAST SENSITIVITY:

1. REFRACTIVE ERRORS

Visibility of low spatial frequencies is not limited by the refractive property of the eye; the refractive errors affect only the higher frequencies.

2. AGE

There occurs a definite decrease in contrast sensitivity with increasing age. It has been reported that from twenties onwards, contrast sensitivity scores for normal population decline with age by about 10% for each decade of life.

3. LENTICULAR CHANGES

Early lens changes can reduce contrast sensitivity essentially for low spatial frequencies. This decrease in contrast sensitivity is not related to the visual acuity.

4.OCULAR AND SYSTEMIC ILLNESS

Contrast sensitivity is also found to be affected by various ophthalmic as well as systemic diseases. It is decreased in cases with retinal , optic nerve and visual pathway diseases, glaucoma, ocular hypertension, retro bulbar neuritis, multiple sclerosis, amblyopia, diabetes mellitus, pituitary adenoma etc.,

MANAGEMENT:

Stopping the offending agent is the first step in managing toxic optic neuropathy. This may cause some reversal of the process. Once the drug is stopped, recovery time varies from weeks to months.

Recovery of vision after stopping ethambutol is still a question. Vision can either drop or remain the same or fail to recover.

Isoniazid-caused toxic neuropathy can either be stabilized or reversed by giving Pyroxidine 25-100mg/day.

Follow up of patients with toxic optic neuropathy is initially done at every 4-6 weeks and then, depending on their recovery, every 6-12 months. At each visit, the following test are to be done :

1. Visual acuity
2. Pupils to be examined
3. Color vision
4. Contrast sensitivity
5. .central fields
6. Optic disc has to be examined.[20]

PROGNOSIS:

Recovery of vision usually happens over several days to weeks in toxic optic neuropathy, once the offending agent is removed.

Prognosis depends on

1. offending agent
2. Total amount of exposure.

Few cases show minimal improvement, few no improvement.[23]

ETHAMBUTOL-INDUCED OPTIC NEUROPATHY

Ethambutol toxicity is frequently described as a dose and duration related optic neuritis that varies in incidence according to the dose of the drug used. The significance of recognizing this entity is that this condition is a potential cause of visual loss in patients undergoing anti-tubercular therapy and warrants a prompt alteration of therapy.[23]

The condition usually develops in the patients taking Ethambutol in doses of 15 to 20 mg/kg/day for 3 to 6 months taken for pulmonary disease. However, it can present earlier or progress more rapidly in patients with renal disease. The condition has also been reported in patients taking standard doses for less duration. Although ethambutol optic neuropathy is thought to be both dose and duration related, there is no definite safe dosage.

Presenting ocular features :

1. Bilateral progressive painless defective vison
2. Decreased color perception
3. Vision drop
4. Both eyes symmetrically involved- no RAPD
5. Central scotoma
6. Bitemporal field defects
7. Peripheral constriction of fields

8. Dyschromatopsia

9. Fundus may remain normal until late stage or may show disc pallor

According to the available reports from literature, testing for the central visual fields, visual evoked potentials and color vision are the most sensitive indicators but in the wake of the fact that the patient may be immobile, it may be difficult for the patient to undergo them.[23]

Tests for color vision may be performed at the bedside. Ishihara's pseudoisochromatic charts may not be the ideal method of assessment as a descriptive study on color vision testing in 42 patients with systemic tuberculosis who received ethambutol, showed. It showed that 15 (36%) patients with high total error scores at the Farnsworth-Munsell 100 test had normal color vision measured by Ishihara pseudo-isochromatic plates. As mentioned above, the earliest field defects may not be actually red-green visual field defects but rather blue-yellow color vision abnormalities.[23]

TREATMENT :

Treatment consists of a cessation of ethambutol. In case any of these above mentioned parameters show derangements, ethambutol should be stopped. Early cessation can help in the recovery of the patient. Many people also advocate stopping isoniazid simultaneously as both can cause optic neuropathy.[26]

Administration of concomitant steroids has neither been proven to be useful nor is indicated keeping in view the possible promotion of the growth of the micro-organisms. Improvement in the visual acuity usually follows a cessation of ethambutol treatment. Rarely, vision continues to deteriorate or vision fails to recover after administration of the drug is stopped. However, contrary to the same, there are some reports which report that there is only a small improvement in visual acuity in such patients.[23]

REVIEW OF LITERATURE

Ethambutol is a well-documented cause of optic neuropathy, with dose-related severity.[25] Ethambutol toxicity has been more pronounced in individuals with decreased zinc levels. Zinc dependant factors are known to preserve mitochondrial homeostatsis. One possibility for ethambutol toxicity is chelation of intracellular zinc.[24]

Christopher et al stated that , " Although EMB-induced optic neuropathy is often reversible, permanent damage may occur at standard doses (15–25 mg/kg/day). Sustained periods of standard loading dose (25 mg/kg/day) have been shown to have a higher incidence of optic neuropathy than therapeutic levels (15 mg/kg/day). It is important to note that visual deficits can occur at any time from 2 to 12 months after initial treatment". [26,27,28]

Ethambutol has been found to be specifically toxic to retinal ganglion cells via an excitotoxic pathway for which endogenous glutamate plays a major role. Also John E Heng et al suggested " glutamate antagonists may be useful in limiting the side effects of ethambutol". [30,31,32]

Eun Ji Lee et al studied " incidence and clinical features of ethambutol-induced optic neuropathy in korea". They did a retrospective chart review of 857 patients who took ethambutol for treatment of tuberculosis identified 89

patients with ethambutol induced optic neuropathy. Ethambutol induced optic neuropathy was diagnosed in 1.5% patients in a follow up of 1 yr +/- 9 months. Based on their study , the incidence of ethambutol induced optic neuropathy in Koreans is estimated to be <2%. Reversibility in visual function after stopping ethambutol is noted in minority of patients. They also found renal dysfunction and daily dose of ethambutol , but not duration of ethambutol treatment , seem to be related to development of Ethambutol Induced Neuropathy. [33]

Hsin-Yi Chen et al did a nationwide population based study on ethambutol induced optic neuropathy. They studied the risk factors and comorbidities associated with ethambutol induced optic neuropathy. They reported "age, hypertension and renal diseases to be risk factors in Taiwanese population. They identified 231 patients newly diagnosed with EON between 2000 and 2008".[34]

Edward G. DeVita et al studied optic neuropathy in Ethambutol – treated renal tuberculosis. They presented two cases of severe ,nonreversible optic neuropathies resulting from the treatment of renal TB with ethambutol at standard doses. They found that the patients with renal TB are at risk to develop bilateral severe and irreversible toxic optic neuropathies. They recommended that ethambutol is not to be used in treatment of renal TB or in any patient with decreased renal function.[35]

Hamzah mustak et al studied ethambutol induced toxic neuropathy in HIV positive patients and found that HIV and, perhaps more importantly, the potential mitochondrial toxic effects of NRTIs may be a risk factor for the development of toxic optic neuropathy from ethambutol therapy via a multiple hit effect. They recommended regular monitoring for HIV positive patients receiving antiretrovirals and requiring ethambutol therapy in order to avoid permanent visual loss.[36]

Alex Melamud et al reported few cases of ocular ethambutol toxicity. Their review of literature revealed that "ethambutol toxicity occurs at the lowest recommended dosage levels and toxicity occurs despite regular monitoring and close medical and ophthalmologic follow up. They also found that ethambutol toxicity can cause severe vision loss that is often permanent and irreversible".[37]

Salmon J F et al studied use of contrast sensitivity in the detection of subclinical ethambutol toxic optic neuropathy and suggested that "Arden contrast sensitivity plates would be effective in detecting subclinical toxic optic neuropathy due to ethambutol and therefore could be used for routine monitoring of ocular function of patients on ethambutol". [39]

Christopher et al studied use of optical coherence tomography in ethambutol induced neuropathy. They found that " OCT showed loss of temporal fibers in patients with ethambutol induced optic neuropathy. They also found OCT can be a valuable tool in the quantitative analysis of optic neuropathies". [39]

R S Behbehani et al reported "mERG abnormalities in the ethambutol treated patients. The N1 amplitude was significantly lower in the ethambutol treated patients than in the control group suggesting Ethambutol is possibly toxic to the retina, and not only the optic nerve. The multifocal ERG may be of value to diagnose and monitor patients taking ethambutol". [40]

Daniel Masvidal et al reported structural-function dissociation in presumed ethambutol optic neuropathy in a 55 yr old male with pulmonary mycobacterium infection. Medications were discontinued. Despite visual improvement after stopping ethambutol disc pallor and RNFL loss in OCT were progressive suggesting persistent structural changes.[41]

TYPE OF STUDY: Hospital based prospective study

OBJECTIVES: To evaluate the

1. Incidence of Ethambutol induced optic neuritis
2. Clinical characteristics of Ethambutol induced optic neuropathy.

Risk factors & dosage information among patients who are treated with Ethambutol for tubercular Uveitis who are attending our Uvea clinic between November 2014 – April 2015

Study Area: Aravind Eye Hospital and post graduate institute of ophthalmology, Madurai.

Study period: November 2014 to april 2015

STUDY SUBJECTS:

Patients who were diagnosed with various forms of intraocular tuberculosis and was started on ethambutol between November 2014 to april 2015 were enrolled for study.

SAMPLE SIZE:

60 patients who were diagnosed with intraocular Tuberculosis and started on Ethambutol from November 2014 to april 2015 (6 months).

PLAN OF WORK

Patients with tubercular uveitis who are treated with ethambutol as part of ATT regime attending our uvea clinic are being screened at first visit followed by 3months after first visit for ethambutol induced optic neuritis.

INCLUSION CRITERIA:

All patients who presented to Uvea clinic of Aravind eye hospital between November 1st 2014 to 31st April 2015 with "definitive clinical signs of intraocular inflammation" compatible with a diagnosis of ocular tuberculosis[5] who were started on ethambutol were included in the study. In our study we followed the guidelines given by Gupta et al for Diagnosis of Intraocular Tuberculosis.

EXCLUSION CRITERIA:

- Best corrected visual acuity <6/36
- Addiction to alcohol/smoking/cannabis
- Decreased vision due to media opacity like cataract and corneal opacity
- Patients diagnosed with glaucoma at the time of initiation of Ethambutol
- Patients diagnosed with optic neuropathy due to other causes like AION, NA-AION, hereditary optic neuropathy, multiple sclerosis.

- Patients with congenital optic disc anomalies
- Patients who are taking amiodarone, Immunosuppressive, anti cancer agents.

CLINICAL EVALUATION

A series of 60 patients who presented to our Uvea clinic who were diagnosed with intraocular Tuberculosis and started on Ethambutol were included in our study. All these patients underwent thorough ophthalmological examination.

The patient's particulars like name , age, sex, weight address were documented in a proforma specially designed for the study and was filled by the examining doctor.

Detailed history of each and every symptom of the patient was taken such as onset , duration of defective vision, progression and associated factors like exposure to any other toxins were documented.

The patients were also enquired about past medical , surgical history, systemic illness, treatment history, personal history and family history and the same was noted.

EACH ONE OF THE PATIENT INCLUDED IN OUR STUDY HAD TO UNDERGO ROUTINE OPHTHALMIC EVALUATION.

- Visual acuity was recorded with snellen's visual acuity chart
- Refraction was done
- Pupillary reaction for normal, sluggish or RAPD was noted

- Anterior segment findings in both eyes were noted with slit lamp biomicroscopy
- Fundus examination was done with 90D- slit lamp followed by indirect ophthalmoscopy
- Type of tubercular Uveitis was determined following the previous tests.
- Special attention was given to the appearance of optic disc
- Color vision was tested using pseudo -isochromatic ishihara color vision chart
- Contrast sensitivity was tested using pelli – robson contrast sensitivity chart
- Central fields were tested using bjerrum screen
- The above tests were repeated in follow up visit
- Montoux test and Systemic examination for primary focus of TB was done.
- Radiological examination like chest x-ray, CT chest, CT abdomen was done to document other focus of TB whenever necessary.
- PCR of ocular fluids to detect Tuberculosis bacilli were done whenever necessary.
- Physician opinion was taken if there was any adverse reaction to drugs during follow up visit and whenever necessary and the treatment was modified accordingly.

- During follow up at 3 months after starting Ethambutol visual acuity, refraction, color vision, contrast sensitivity, central fields, anterior and posterior segment evaluation with slit lamp biomicroscopy and indirect ophthalmoscopy was repeated.
- Enquiry in to Adherence to treatment and any adverse reaction to drugs were done and physician opinion was taken if necessary.
- The incidence of Ethambutol induced optic neuropathy and it's clinical profile was analyzed.

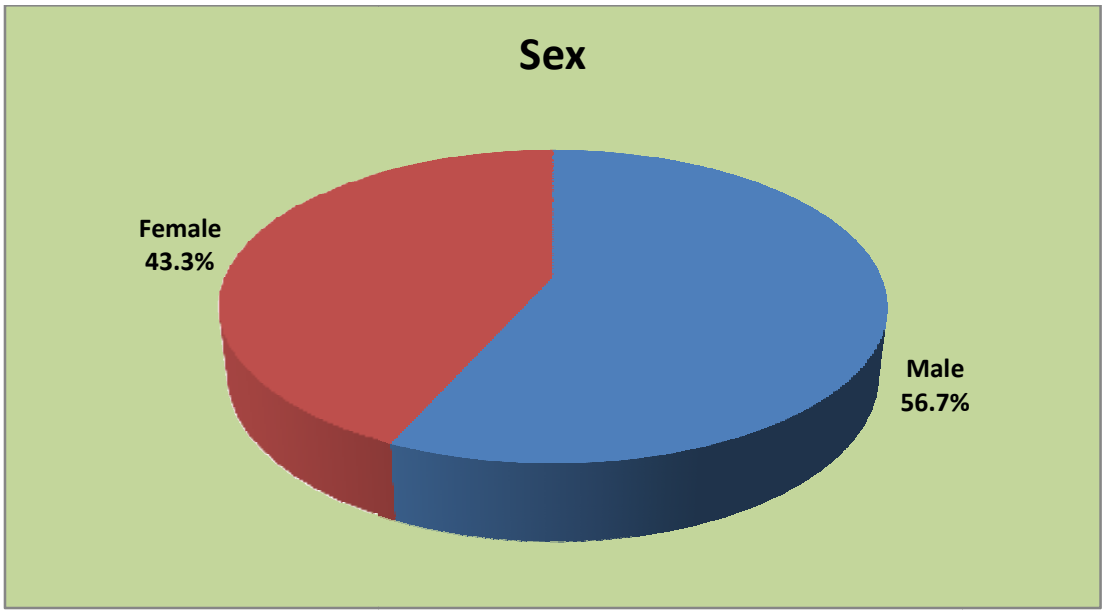
RESULTS

AGE

The Mean (SD) of the age is 46.6(12.8) years & its range is 13 - 66 years

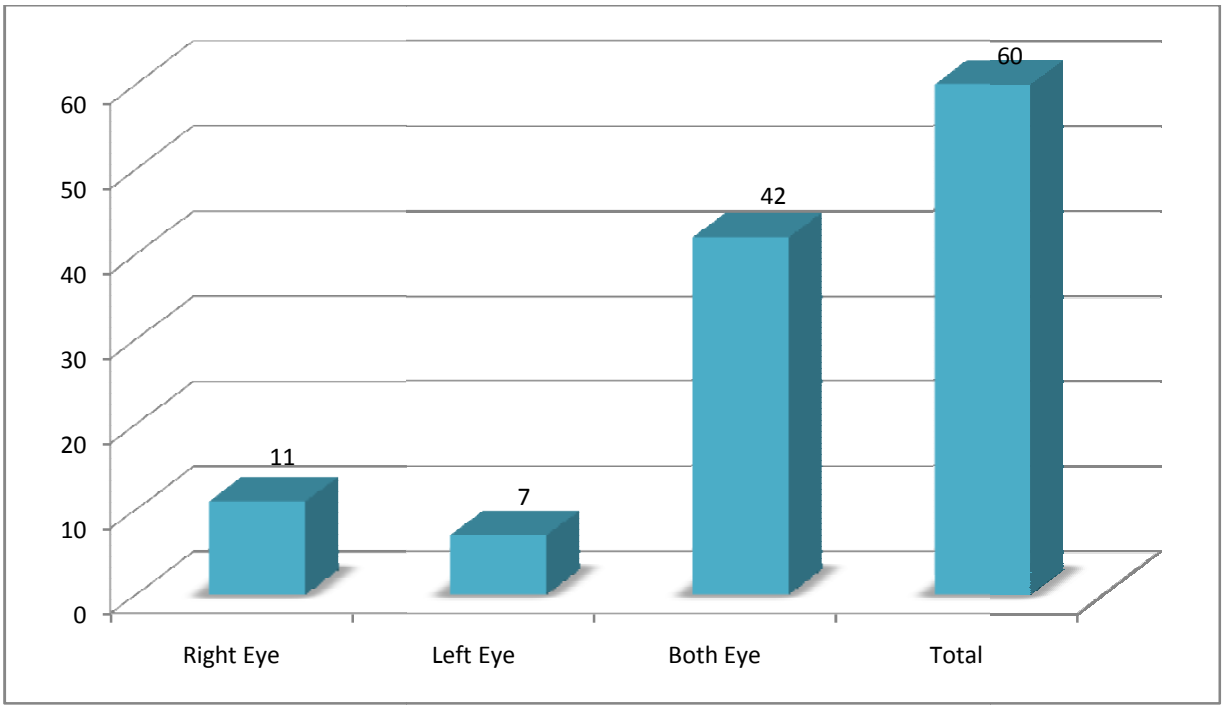
SEX

Sex	n	%
Male	34	56.7
Female	26	43.3
Total	**60**	**100**



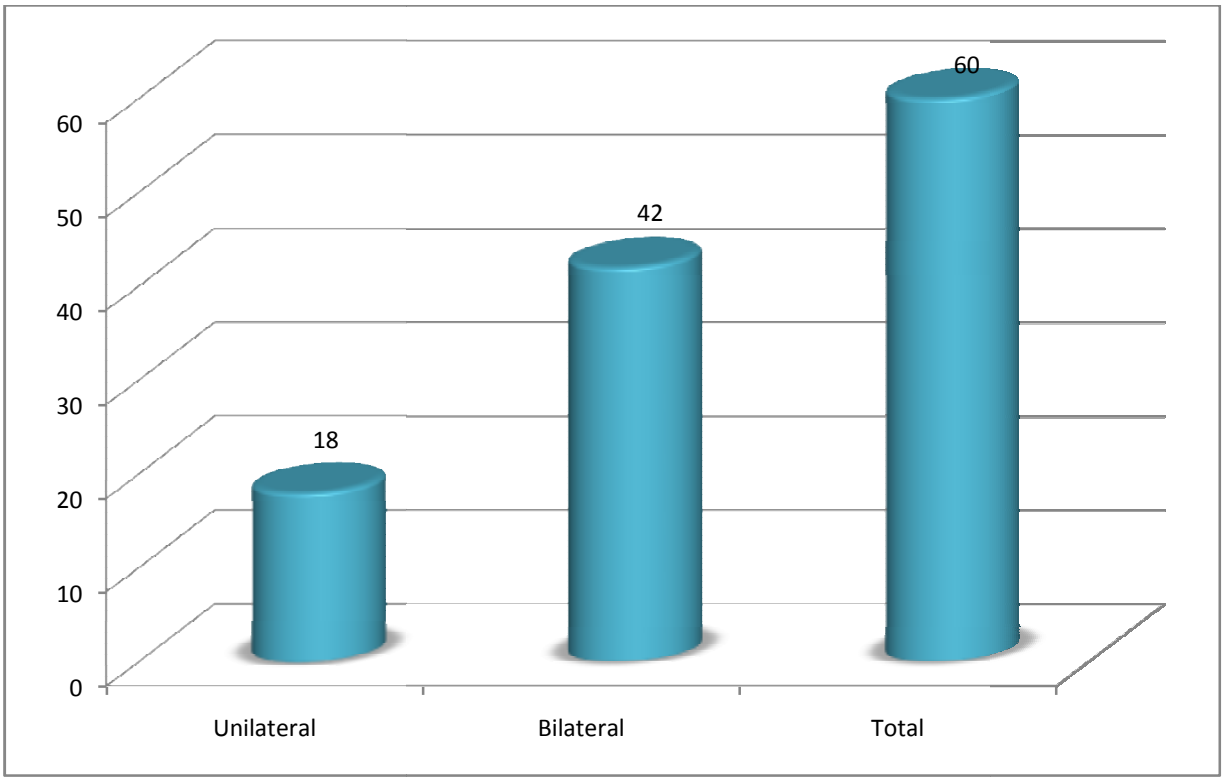
EYE

Eye	n	%
Right Eye	11	18.3
Left Eye	7	11.7
Both Eye	42	70.0
Total	**60**	**100**



LATERALITY

Laterality	n	%
Unilateral	18	70.0
Bilateral	42	30.0
Total	**60**	**100**

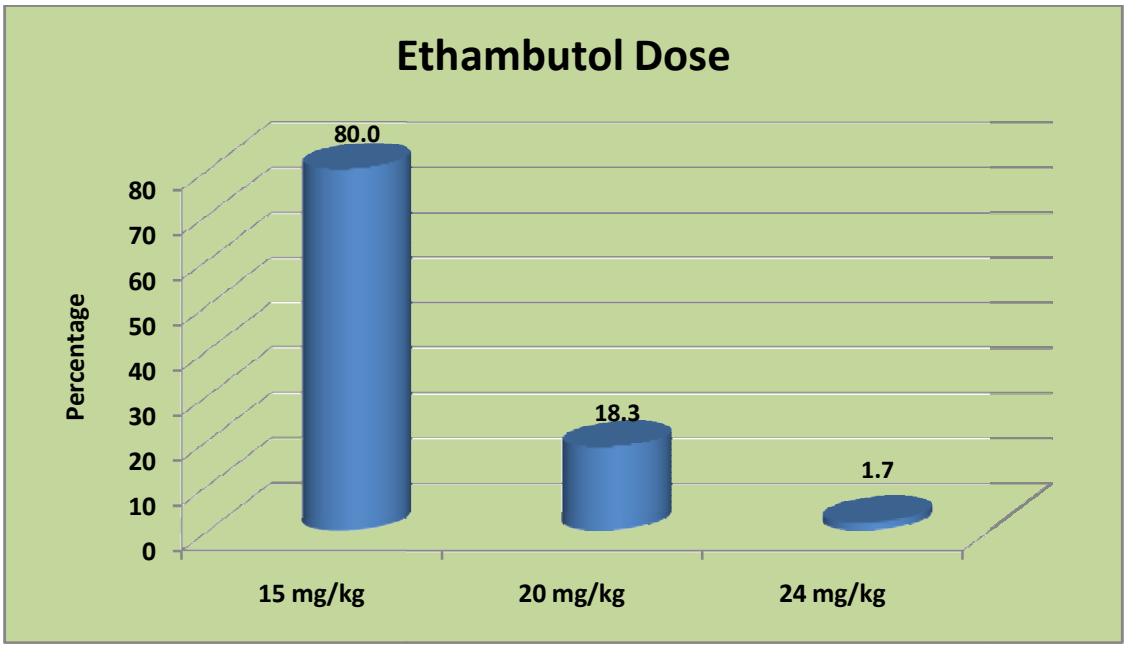


WEIGHT

The Mean (SD) of the weight is 61.47(6.4) kg & its range is 45 - 77 kg

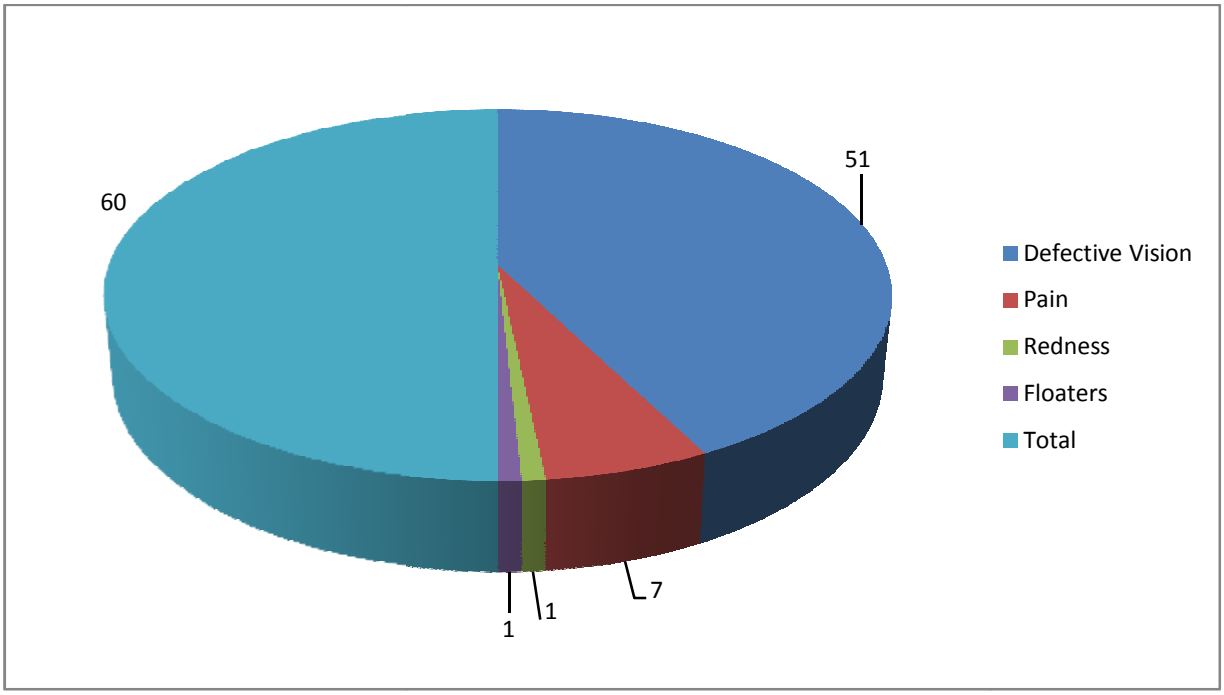
ETHAMBUTOL DOSE

EthambutolDose	**n**	**%**
15*mg/kg*	48	80.0
20 *mg/kg*	11	18.3
24 *mg/kg*	1	1.7
Total	**60**	**100**



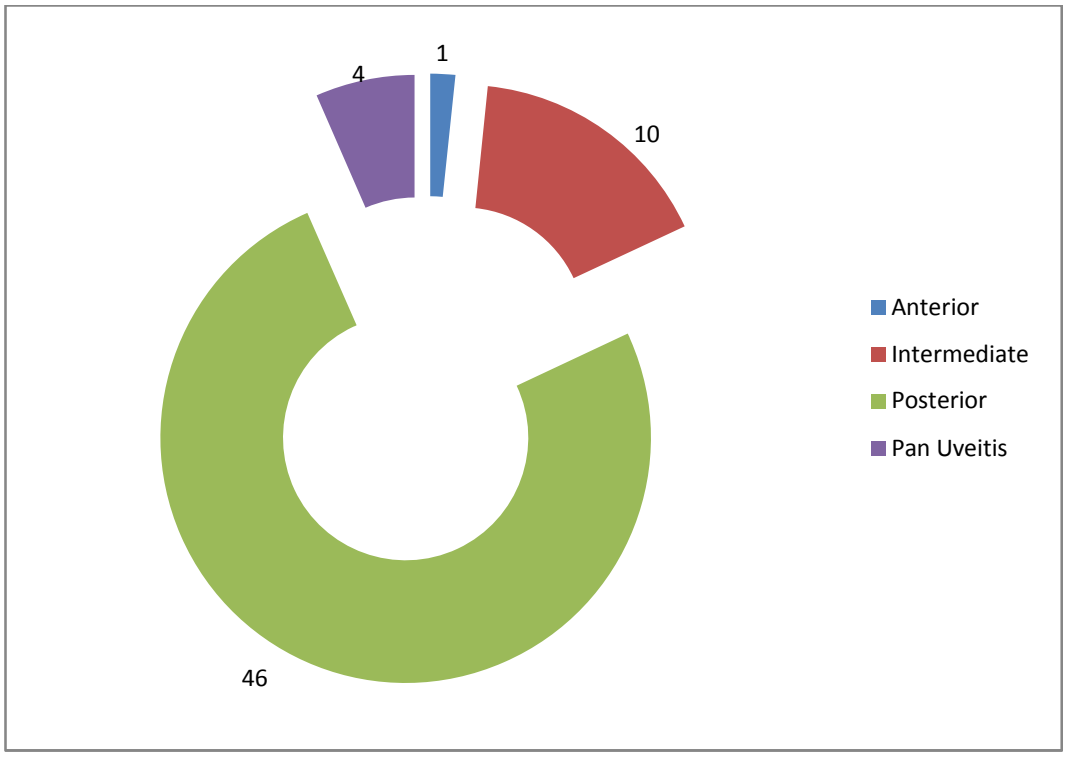
COMPLAINTS

Complaints	n	%
Defective Vision	51	85.0
Pain	7	11.7
Redness	1	1.7
Floaters	1	1.7
Total	**60**	**100**



TYPES OF UVEITIS

Types of Uveitis	n	%
Anterior	1	1.7
Intermediate	10	17.0
Posterior	46	76.7
Pan Uveitis	4	6.7

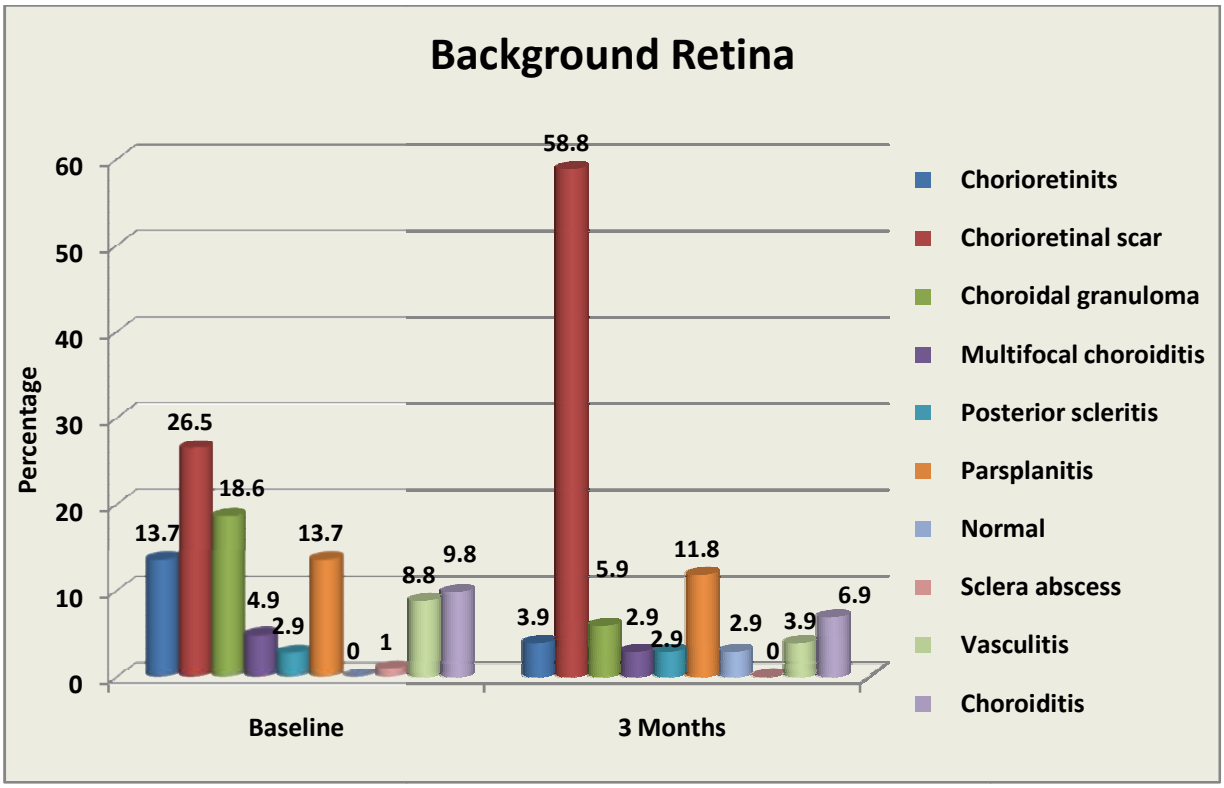


PAST HISTORY

Past history	n	%
Hypertension	3	5.0
Diabetes	1	1.7
Nil	57	95.0

Parameters	Visit1	Visit2
Colour Vision	**(n=102)**	**(n=102)**
Normal	90(88.2)	100(98.0)
Missing	12(11.8)	2(2.0)
Contrast Sensitivity	**(n=102)**	**(n=102)**
Normal	90(88.2)	98(96.0)
Missing	12(11.8)	4(4.0)
Central Fields	**(n=102)**	**(n=102)**
Normal	90(88.2)	99(97.0)
Missing	12(11.8)	3(3.0)
Background Retina	**(n=102)**	**(n=102)**
Chorioretinits	14(13.7)	4(3.9)
Chorioretinal scar	27(26.5)	60(58.8)
Choroidal granuloma	19(18.6)	6(5.9)
Multifocal choroiditis	5(4.9)	3(2.9)
Posterior scleritis	3(2.9)	3(2.9)
Parsplanitis	14(13.7)	12(11.8)
Normal	-	3(2.9)
Sclera abscess	1(1.0)	-
Vasculitis	9(8.8)	4(3.9)
Choroiditis	10(9.8)	7(6.9)

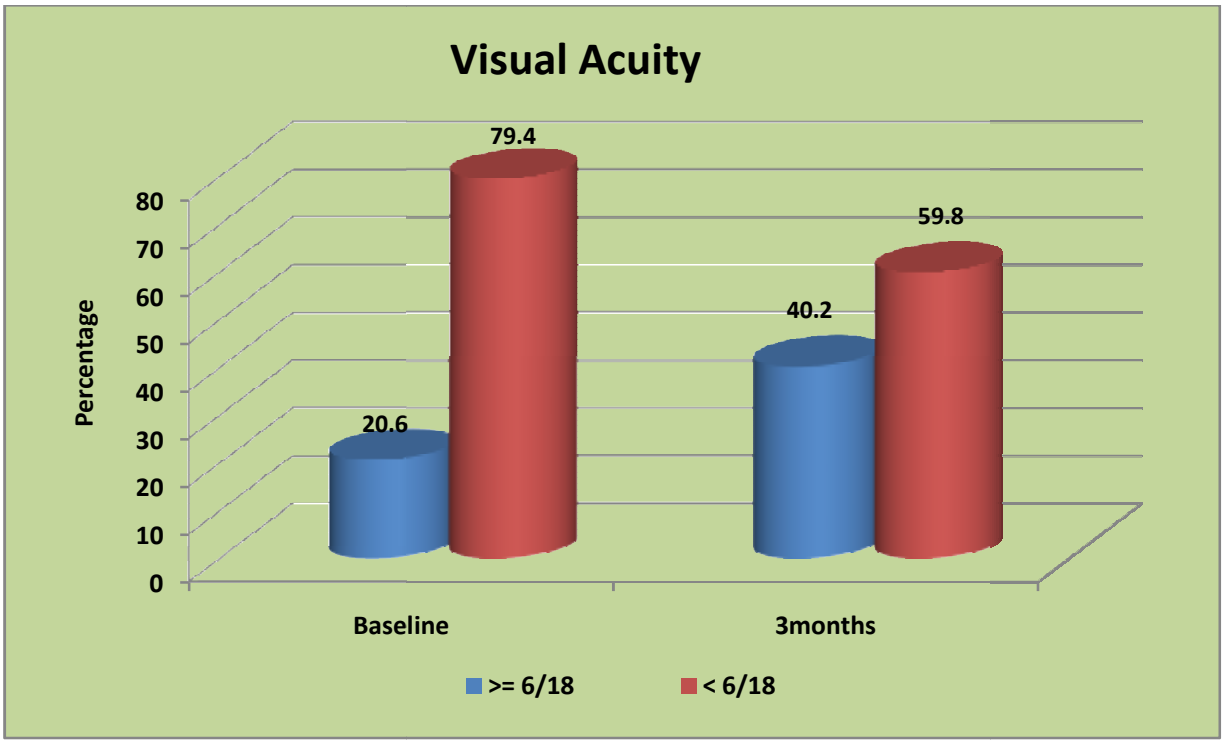
Optic Nerve Head	**(n=102)**	**(n=102)**
Normal	99(97.0)	99(97.0)
Pallor	1(1.0)	1(1.0)
Edema	1(1.0)	1(1.0)
Hyperemia	1(1.0)	1(1.0)
Focus of TB	**(n=60)**	
Lymph node	8(13.3)	
Lung	40(66.7)	-
Abdomen	12(20.0)	
Spine	-	
OCT		**(n=60)**
Yes	-	-
No		60(100)



VISUAL ACUITY

Visual Acuity	n	Median (Snellen's Equivalent)	Mean(SD)	Range	P - value*
Visit1	102	0.78(6/36)	0.68(0.26)	6/6 - 1/60	<0.0001
Visit2	102	0.60(6/24)	0.56(0.21)	6/6 - 6/60	

*Paired t-Test



DISCUSSION

In our study we studied 60 patients who were diagnosed with various forms of intraocular tuberculosis who were given ethambutol for 2 months in a dose range of 15-24mg/kg. There was nil incidence of ethambutol induced optic neuropathy among our patients. The Mean age of the patients included in our study was 46.6 years and the SD was 12.8 years. The mean dose of ethambutol was 16 mg/kg/day. The mean duration of ethambutol in our study was 2 months.

In general ethambutol induced optic neuropathy is considered to be both dose and duration related. **Eun ji lee et al** studied the incidence and clinical features of ethambutol induced optic neuropathy by doing a retrospective chart review of 857 patients. They found ethambutol induced optic neuropathy was found in 13 patients during follow up period of 12 +/- 9 months. In our study we followed up the patient until 3 months after starting on ethambutol since the incidence of ethambutol induced optic neuropathy was high at 3 months of starting theraphy.

The average dose of ethambutol used in the study conducted by eun Ji Lee was 17+/- 2.21 mg/kg/day, and the duration of therapy was 9.38 +/10 months. They reported a incidence of <2% in Koreans.

In our study the average dose used was 16 mg/kg and the duration of therapy was 2 months. Less duration of therapy might explain the nil incidence of ethambutol induced optic neuropathy in our study. Also the study conducted by Eun Ji Lee et al had longer follow up record and larger sample size.

However **Carr RE et al and Karmon G et al** reported that ethambutol induced optic neuropathy develops from 15 days to 2 yrs after initiation of ethambutol treatment. The mean interval between starting medication and documentation of ethambutol induced optic neuropathy was found to be 3.4 months to 5 months. But in the study conducted by **Eun Ji Lee et al** found the visual symptoms to have developed at 7.3 months +/- 9.45 months after treatment. In our study most patients received dose of 15 mg/kg/day for 2months. Few patients received 20mg/kg for 2 months.

Citron et al and **leiboid et al** found that the estimated risk of ethambutol induced ocular toxicity falls below 1% when standard dose of 15mg/kg is used which coincides with results in our study since in our study we used standard dose of 15mg/kg/day for 2 months duration[42].

In our study we didn't have patients with renal dysfunction.

De Vita EG et al reported that impaired renal function was related to ethambutol induced optic neuropathy. Some investigators believe that patients

with renal dysfunction have inappropriate drug levels and hence at higher risk of developing ethambutol induced optic neuropathy.

In our study none of the patients with hypertension developed optic neuropathy. **Hsin-Yi Chen et al** did a nationwide population – based study and investigated risk factors and comorbidities associated with ethambutol induced optic neuropathy. They found hypertension to be a risk factor for development of ethambutol optic neuropathy .

In our study the patients were given ethambutol for 2 months duration. In the study by **Hsin-Yi Chen et al ,** they found that patients who were prescribed ethambutol more than 3 months were found to be at a mild elevated risk of ethambutol induced optic neuropathy when compared to patients who were prescribed ethambutol for less than 3 months(OR = 1.38, 95% CI 1.02 to 1.86).

CONCLUSION

In our study, Standard dose of Ethambutol given for duration of 2 months is found to be safe. In our study, patients were given standard dose of Ethambutol for 2 months as part of treatment of Tubercular Uveitis and we found that there was no incidence of Ethambutol Optic Neuropathy.

LIMITATIONS

1. Shorter follow up period.

2. Small sample size.

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PROFORMA

Name: MR NO:

Age: case no:

Sex: Male/female male :1; ☐ female:2 ☐
weight :

residential address:

duration of ATT:

type of uveitis:

anterior/intermediate/posterior/pan Uveitis

anterior:1 ☐

intermediate:2 ☐

posterior :3 ☐

pan Uveitis:4 ☐

ethambutol dose : _____/kg

complaints:

defective vision:1 ☐; pain:☐ 2;redness:☐ 3;combined: ☐ 4;floaters: ☐5

1.defective vision:

Duration

sudden/insidious

painless/painful

altered/decreased colour vision: y/n

history suggestive of field defects: y/n

past history:

systemic hypertension :1 ☐

renal disease :2 ☐

diabetes:3 ☐

glaucoma:4 ☐

nil : 5 ☐

personal history:

h/o alcohol : y/n if yes:1 ☐

h/o smoking : y/n if yes:2 ☐

nil : 3 ☐

treatment history:

h/o intake of other medications:

if yes :1

if no :2

ocular examination: **re** **le**

bcva:

anterior segment:

pupil:

normal/sluggish/RAPD

colour vision:

normal :1

abnormal :2

central fields:

normal:1

abnormal:2

contrast sensitivity:

normal:1

abnormal:2

fundus:

media: clear/haze

optic nerve head:

normal looking/pallor/edema/others

normal:1 ☐

pallor:2 ☐

edema:3 ☐

hyperemia:4 ☐

macula:

foveal reflex: present/dull

background retina:

chorioretinits:1 ☐

chorioretinal scar:2 ☐

choroidal granuloma:3 ☐

multifocal choroiditis:4 ☐

posterior scleritis :5 ☐

parsplanitis : 6 ☐

normal :7 ☐

sclera abscess:8 ☐

vasculitis :9 ☐

choroiditis: 10 ☐

others:

investigations:

focus of TB: lymph node :1; lung:2; abdomen :3; spine :4

sd-oct: report if done for the case

yes :1

no :2

ABBREVIATION

WHO	-	World Health Organization
ART	-	Anti Retroviral Therapy
ATT	-	Anti Tubercular Therapy
PCR	-	Polymerase Chain Reaction
HIV	-	Human Immunodeficiency Virus
AIDS	-	Acquired Immunodeficiency Syndrome
CME	-	Cystoid Macular Edema

ARAVIND MEDICAL RESEARCH FOUNDATION
Institutional Ethics Committee
(Registration No.ECR/182/Inst/TN/2013 dated 20.04.2013)

6th February 2015

To

Dr.Swathija B
MS Resident
Aravind Eye Hospital
Madurai

Dear Dr. Swathija,

Thesis Title: Incidence and clinical features of Ethambutol- Induced Optic Neuropathy in Tubercular Uveitis Patients

IRB Code: IRB201400177

Thank you for submitting your thesis and seeking the approval from the ethics committee. The documents provided by you for consideration which include the thesis protocol and informed consent forms were reviewed for the research methodology and scientific content. The Ethical committee did not find any correction and has recommended the thesis to go ahead in the present form.

Thanking you

Yours Sincerely,

S. Lalitha

Dr.Lalitha Prajna
Member Secretary
Institutional Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
ARAVIND MEDICAL RESEARCH FOUNDATION
No.1, Anna Nagar, Madurai-625 020


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INTRODUCTION

MASTER CHART

S.No	NAME	MR.NO	AGE	SEX	DOV 1	WEIGHT	DURATION OF ETL	ETL DOSE	COMPLAINTS	TYPE OF UVEITIS	PAST HISTORY	PERSONAL HISTORY	TREATMENT HISTORY	VA RE	VA LE	CV RE	CV LE	CS RE	CS LE	CF RIGHT	CF LEFT	F RE	F LE	ONH RE	ONH LE	FOCUS OF TB	DOV 2	VA RE	VA LE	CV RE	CV LE	CS RE	CS LE	CF RIGHT	CF LEFT	F RE	F LE	ONH RE	ONH LE	OCT
1	akash sunil	3889018	13	2	nov-14	52 kg	2 months	15 mg/kg	1	2	5	3	2	4/60	6/6	1	1	1	1	1	1	6	7	1	1	2	feb-15	6/18	6/6	1	1	1	1	1	1	6	7	1	1	2
2	sankari	3894414	35	2	nov-14	60 KG	2 months	15mg/kg	1	3	5	3	2	5/60	6/36		1		1		1	1	2	1	2	2	feb-15	6/36	6/6		1		1		1	1	2	1	2	2
3	rahima	3862286	45	2	nov-14	65 kg	2 months	24 mg/kg	1	4	1	3	2	6/60	6/18		1		1		1	2	2	4	1	2	feb-15	6/60	6/18		1		1		1	2	2	4	1	2
4	beeran koya	3832493	47	1	nov-14	66 kg	2months	15 mg/kg	5	4	1	3	2	6/6	6/6	1	1	1	1	1	1	1	1	1	3	1	feb-15	6/6	6/6	1	1	1	1	1	1	2	1	1	3	2
5	rajeswari	3772341	66	2	nov-14	45 kg	2 months	15 mg/kg	3	4	5	3	2	6/24	6/6	1		1	1	1	1	1	7	1	1	2	feb-15	6/18	6/6	1	1	1	1	1	1	1	7	1	1	2
6	sivasudharsan	3877392	18	1	nov-14	45 kg	2 months	15 mg/kg	1	4	5	3	2	6/6	6/18	1	1	1	1	1	1	7	1	1	1	2	feb-15	6/6	6/18	1	1	1	1	1	1	7	1	1	1	2
7	soundarapandian	3880219	64	1	nov-14	77kg	2 months	15 mg/kg	1	3	1,3	3	2	6/18	6/6	1	1	1	1	1	1	4	7	1	1	2	feb-15	6/18	6/6	1	1	1	1	1	1	4	7	1	1	2
8	chinnasamy	3659885	23	1	nov-14	60 kg	2 months	15 mg/kg	1	3	5	3	2	6/36	1/60	1		1		1		2	3	1	1	2	feb-15	6/24	6/12	1	1	1	1	1	1	2	2	1	1	2
9	nupur chandra	3908664	29	2	nov-14	55 kg	2months	15 mg/kg	1	3	5	3	2	6/12	6/24	1	1	1	1	1	1	1	1	1	1	3	feb-15	6/12	6/12	1	1	1	1	1	1	2	2	1	1	2
10	naveen c	3865455	27	1	nov-14	60 kg	2 months	15 mg/kg	1	3	5	3	2	6/9	6/12	1	1	1	1	1	1	2	1	1	1	2	feb-15	6/9	6/9	1	1	1	1	1	1	2	2	1	1	2
11	murugan p	3797208	63	1	nov-14	65 kg	2months	15 mg/kg	1	3	5	3	2	6/12	6/36	1	1	1	1	1	1	2	1	1	1	3	feb-15	6/12	6/12	1	1	1	1	1	1	2	2	1	1	2
12	sarasu m	3466992	45	2	dec-14	65 kg	2 months	15 mg/kg	2	3	5	3	2	6/12	6/24	1	1	1	1	1	1	7	8	1	1	2	mar-15	6/12	6/12	1	1	1	1	1	1	7	7	1	1	2
13	azis kumar k	3496683	30	1	dec-14	70 kg	2 months	15 mg/kg	1	3	5	3	2	6/9	6/12	1	1	1	1	1	1	7	9	1	1	2	mar-15	6/9	6/9	1	1	1	1	1	1	7	9	1	1	2
14	krishnan a	3489883	45	1	dec-14	60 kg	2months	15 mg/kg	1	1 ,2	5	3	2	6/9	6/9	1	1	1	1	1	1	6	6	1	1	3	mar-15	6/9	6/9	1	1	1	1	1	1	7	7	1	1	2
15	sampath s	3914363	56	1	dec-14	75 kg	2months	15 mg/kg	1	3	5	3	2	6/36	6/24	1	1	1	1	1	1	10	10	1	1	2	mar-15	6/24	6/24	1	1	1	1	1	1	2	2	1	1	2
16	jayaprada	3896610	57	2	dec-14	65 kg	2months	15 mg/kg	1	2	5	3	2	6/24	6/24	1	1	1	1	1	1	6	6	1	1	2	mar-15	6/12	6/12	1	1	1	1	1	1	6	6	1	1	2
17	pushpa	3713226	52	2	dec-14	65 kg	2months	15 mg/kg	1	3	5	3	2	6/36	6/60	1		1		1		10	10	1	1	2	mar-15	6/36	6/36	1	1	1	1	1	1	10	10	1	1	2
18	saraswathi	3767194	55	2	dec-14	60 kg	2months	15 mg/kg	1	3	5	3	2	6/24	6/24	1	1	1	1	1	1	3	3	1	1	2	mar-15	6/24	6/24	1	1	1	1	1	1	2	2	1	1	2
19	karuppusamy m	3847545	55	1	dec-14	72 kg	2months	15 mg/kg	1	3	5	3	2	6/9	6/9	1	1	1	1	1	1	9	9	1	1	3	mar-15	6/9	6/9	1	1	1	1	1	1	9	9	1	1	2
20	ummal basiriya	3867539	49	1	dec-14	64 kg	2months	20mg/kg	1	2	5	3	2	6/60	6/36		1		1		1	6	6	1	1	2	mar-15	6/36	6/36	1	1	1	1	1	1	6	6	1	1	2
21	jaburuth nisha	3875966	47	2	dec-14	55 kg	2months	20mg/kg	1	2	5	3	2	6/12	6/60	1		1		1		10	10	1	1	2	mar-15	6/12	6/36	1	1	1	1	1	1	10	10	1	1	2
22	thennarasu	3479619	46	1	dec-14	65 kg	2months	15mg/kg	1	2	5	3	2	6/18	6/36	1	1	1	1	1	1	6	6	1	1	3	mar-15	6/18	6/36	1	1	1	1	1	1	6	6	1	1	2
23	sirajun	3772107	23	1	jan-15	55 kg	2months	15mg/kg	1	3	5	3	2	6/36	6/36	1	1	1	1	1	1	2	1	1	1	3	apr-15	6/18	6/18	1	1	1	1	1	1	2	2	1	1	2
24	nagarajan	3948544	35	1	jan -15	60 Kg	2months	20mg/kg	1	3	5	3	2	6/24	6/24	1	1	1	1	1	1	6	6	1	1	3	apr-15	6/18	6/18	1	1	1	1	1	1	6	6	1	1	2
25	anandhi	3954241	50	2	jan-15	55 kg	2months	15mg/kg	2	3	5	3	2	6/36	6/36	1	1	1	1	1	1	9	9	1	1	3	apr-15	6/18	6/18	1	1	1	1	1	1	2	2	1	1	2
26	papathi	3950140	55	2	jan-15	65 kg	2months	15mg/kg	1	3	5	3	2	6/60	6/36		1		1		1	10	2	1	1	3	apr-15	6/60	6/36	1	1	1	1	1	1	2	2	1	1	2
27	ansabraham	3953234	45	1	jan -15	70kg	2months	20mg/kg	2	3	5	3	2	6/36	6/36	1	1	1	1	1	1	3	2	1	1	3	apr-15	6/24	6/36	1	1	1	1	1	1	2	2	1	1	2
28	ravichandran	3954667	65	1	jan-15	65kg	2months	15mg/kg	1	2	5	3	2	6/60	6/36		1		1		1	4	7	1	1	2	apr-15	6/36	6/36	1	1	1	1	1	1	2	7	1	1	2
29	jesudas	3956640	55	1	feb-15	75 kg	2months	15mg/kg	1	3	5	3	2	6/36	6/36	1	1	1	1	1	1	9	9	1	1	2	may-15	6/36	6/36	1	1	1	1	1	1	2	2	1	1	2
30	amsath begum	3826142	35	2	feb 15	60 kg	2months	15mg/kg	1	3	5	3	2	6/36	6/24	1	1	1	1	1	1	10	2	1	1	2	may-15	6/36	6/24	1	1	1	1	1	1	10	2	1	1	2
31	suresh	3901970	45	1	feb 15	64 kg	2months	15mg/kg	2	3	5	3	2	6/9	6/24	1	1	1	1	1	1	7	5	1	1	2	may-15	6/9	6/18	1	1	1	1	1	1	7	5	1	1	2
32	yasoda	3466925	54	2	feb 15	57 kg	2months	20mg/kg	2	3	5	3	2	6/24	6/9	1	1	1	1	1	1	5	7	1	1	2	may-15	6/18	6/9	1	1	1	1	1	1	5	7	1	1	2
33	selvi	3664785	36	2	feb 15	62kg	2months	15mg/kg	1	3	5	3	2	6/36	6/9	1	1	1	1	1	1	4	7	1	1	3	may-15	6/36	6/9	1	1	1	1	1	1	4	7	1	1	2
34	anbujothy	3972421	42	2	feb 15	64 kg	2months	15mg/kg	1	3	5	3	2	6/24	6/24	1	1	1	1	1	1	3	2	1	1	2	may-15	6/24	6/24	1	1	1	1	1	1	3	2	1	1	2
35	shalini p	3041593	54	2	feb 15	70kg	2months	15mg/kg	1	3	5	3	2	6/9	6/36	1	1	1	1	1	1	7	3	1	1	3	may-15	6/9	6/36	1	1	1	1	1	1	7	3	1	1	2
36	mali.s.k	3968311	62	1	feb 15	65kg	2months	15mg/kg	1	3	5	3	2	6/36	6/36	1	1	1	1	1	1	2	4	1	1	2	may-15	6/36	6/36	1	1	1	1	1	1	2	4	1	1	2
37	lakshmi	3462800	64	2	feb 15	54kg	2months	15mg/kg	1	3	5	3	2	6/18	6/24	1	1	1	1	1	1	2	3	1	1	2	may-15	6/18	6/18	1	1	1	1	1	1	2	2	1	1	2
38	nagaraj	3962956	62	1	feb 15	60kg	2months	20mg/kg	1	3	5	3	2	6/24	6/24	1	1	1	1	1	1	3	3	1	1	2	may-15	6/24	6/24	1	1	1	1	1	1	3	3	1	1	2
39	mahadevi	3739989	60	2	feb 15	65kg	2months	15mg/kg	2	3	5	3	2	6/36	6/36	1	1	1	1	1	1	9	2	1	1	2	may-15	6/36	6/36	1	1	1	1	1	1	9	2	1	1	2
40	maheswaran	3565302	27	1	feb 15	55kg	2months	20mg/kg	1	3	5	3	2	6/24	6/36	1	1	1	1	1	1	3	3	1	1	2	may-15	6/24	6/24	1	1	1	1	1	1	2	2	1	1	2
41	uma	3777466	35	2	feb 15	60kg	2months	15mg/kg	1	2	5	3	2	6/36	6/60	1		1		1		2	6	1	1	1	may-15	6/36	6/24	1	1	1	1	1	1	2	6	1	1	2
42	audiammal	3593317	60	2	feb 15	55kg	2months	20mg/kg	1	3	5	3	2	6/36	6/36	1	1	1	1	1	1	3	2	1	1	2	may-15	6/36	6/36	1	1	1	1	1	1	2	2	1	1	2
43	lalam pullaiah	3978798	60	1	mar-15	54kg	2months	15mg/kg	1	3	5	3	2	6/24	6/36	1	1	1	1	1	1	2	1	1	1	2	jun-15	6/24	6/36	1	1	1	1	1	1	2	2	1	1	2
44	raji c	3979059	55	2	mar-15	65 kg	2months	15mg/kg	1	3	5	3	2	6/36	6/9	1	1	1	1	1	1	3	7	1	1	2	jun-15	6/24	6/9	1	1	1	1	1	1	3	7	1	1	2
45	pandiarajan	3975551	45	1	mar-15	64 kg	2months	15mg/kg	1	3	5	3	2	6/18	6/36	1	1	1	1	1	1	2	4	1	1	2	jun-15	6/18	6/36	1	1	1	1	1	1	2	2	1	1	2
46	radha krishnan	2670208	57	1	mar-15	58kg	2months	15mg/kg	1	3	5	3	2	6/36	6/24	1	1	1	1	1	1	3	2	1	1	2	jun-15	6/24	6/24	1	1	1	1	1	1	2	2	1	1	2

47	suresh	2645794	45	1	mar-15	55kg	2months	20mg/kg	1	3	5	3	2	6/24	6/18	1	1	1	1	1	1	10	2	1	1	2	jun-15	6/24	6/18	1	1	1	1	1	1	10	2	1	1	2
48	yusef sheik	3981088	56	1	mar-15	65kg	2months	15mg/kg	1	3	5	3	2	6/36	6/24	1	1	1	1	1	1	3	2	1	1	1	jun-15	6/24	6/24	1	1	1	1	1	1	2	2	1	1	2
49	noorun nasreema	3962342	55	2	mar-15	65kg	2months	15mg/kg	1	3	5	3	2	6/36	5/60	1		1		1		2	1	1	1	2	jun-15	6/36	6/36	1		1		1		2	2	1	1	2
50	ramasamy	3280161	45	1	mar-15	60kg	2months	15mg/kg	1	3	5	3	2	6/36	6/9	1	1	1	1	1	1	3	7	1	1	2	jun-15	6/24	6/9	1	1	1	1	1	1	2	7	1	1	2
51	mahadevi	3739989	35	2	mar-15	58 kg	2months	15mg/kg	1	2	5	3	2	6/36	6/6	1	1	1	1	1	1	6	7	1	1	2	jun-15	6/24	6/6	1	1	1	1	1	1	6	7	1	1	2
52	munevarrah	3400618	60	1	mar-15	60kg	2months	15mg/kg	1	3	5	3	2	6/6	6/36	1	1	1	1	1	1	7	3	1	1	1	jun-15	6/6	6/24	1	1	1	1	1	1	7	3	1	1	2
53	prabhu	3358130	55	1	apr-15	55kg	2months	15mg/kg	1	3	5	3	2	5/60	6/24		1		1		1	9	2	1	1	2	jul-15	6/36	6/24	1	1	1	1	1	1	2	2	1	1	2
54	selvam	3474085	57	1	apr-15	65kg	2months	15mg/kg	2	3	5	3	2	6/6	6/24	1	1	1	1	1	1	7	5	1	1	1	jul-15	6/6	6/18	1	1	1	1	1	1	7	5	1	1	2
55	mariammal	3968875	45	2	apr-15	67kg	2months	15mg/kg	1	3	5	3	2	6/18	6/36	1	1	1	1	1	1	2	3	1	1	1	jul-15	6/18	6/18	1	1	1	1	1	1	2	2	1	1	2
56	balasubramani	3472470	35	1	apr-15	55kg	2months	20mg/kg	1	3	5	3	2	6/36	6/9	1	1	1	1	1	1	1	7	1	1	1	jul-15	6/24	6/9	1	1	1	1	1	1	2	7	1	1	2
57	vijayaraja	3989134	45	1	apr-15	60kg	2months	15mg/kg	1	3	5	3	2	6/24	6/24	1	1	1	1	1	1	3	2	1	1	1	jul-15	6/24	6/24	1	1	1	1	1	1	2	2	1	1	2
58	krishnamoorthy	3904707	40	1	apr-15	65kg	2months	15mg/kg	1	3	5	3	2	6/60	6/36		1		1		1	1	2	1	1	2	jul-15	6/36	6/36	1	1	1	1	1	1	2	2	1	1	2
59	anuradha	3019903	45	2	apr-15	55kg	2months	20mg/kg	1	2	5	3	2	6/18	6/9	1	1	1	1	1	1	6	7	1	1	2	jul-15	6/18	6/9	1	1	1	1	1	1	6	7	1	1	2
60	mathan	3846722	30	1	apr-15	60kg	2months	15mg/kg	1	3	5	3	2	6/24	6/36	1	1	1	1	1	1	2	10	1	1	2	jul-15	6/24	6/24	1	1	1	1	1	1	2	10	1	1	2